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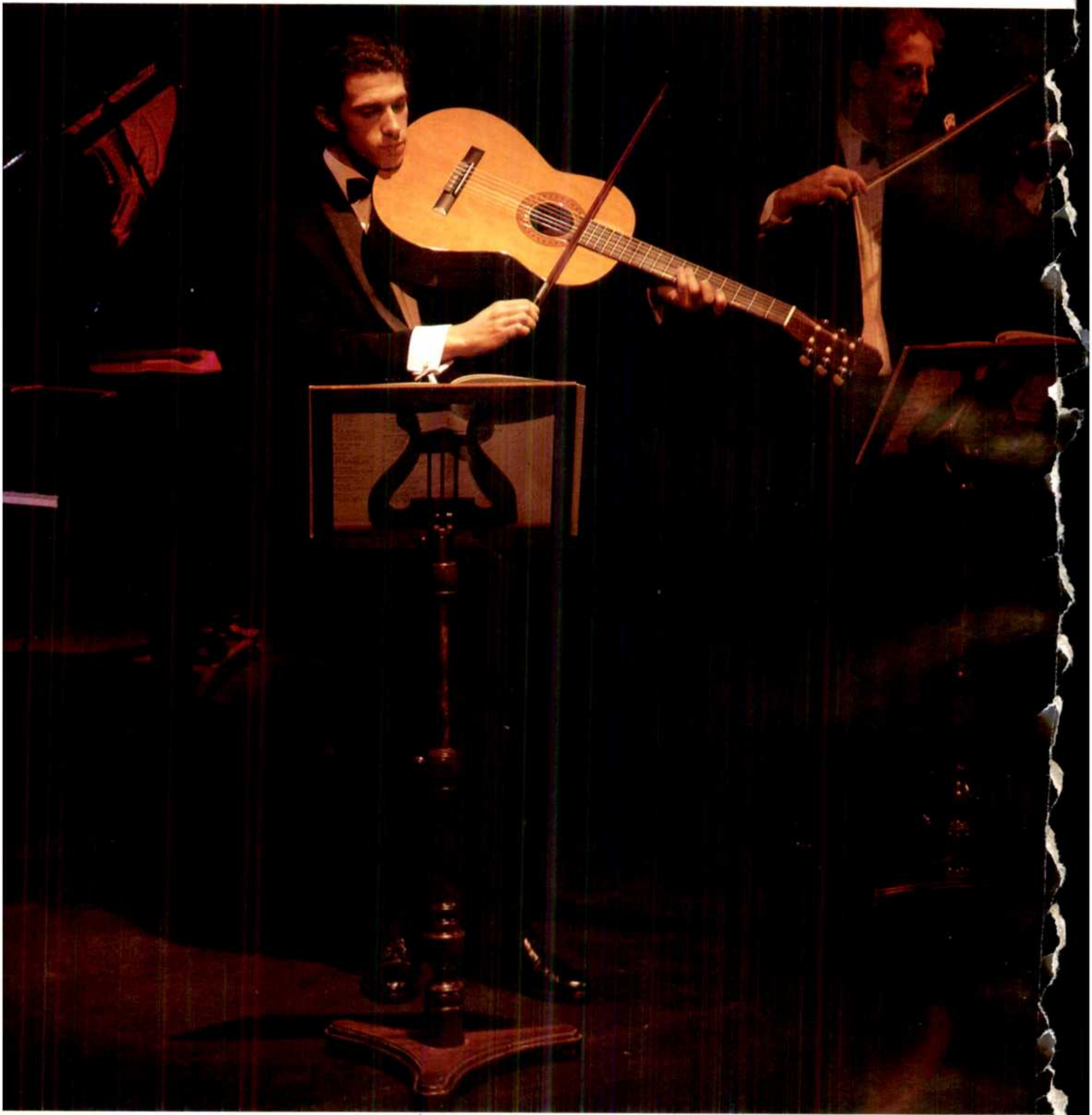

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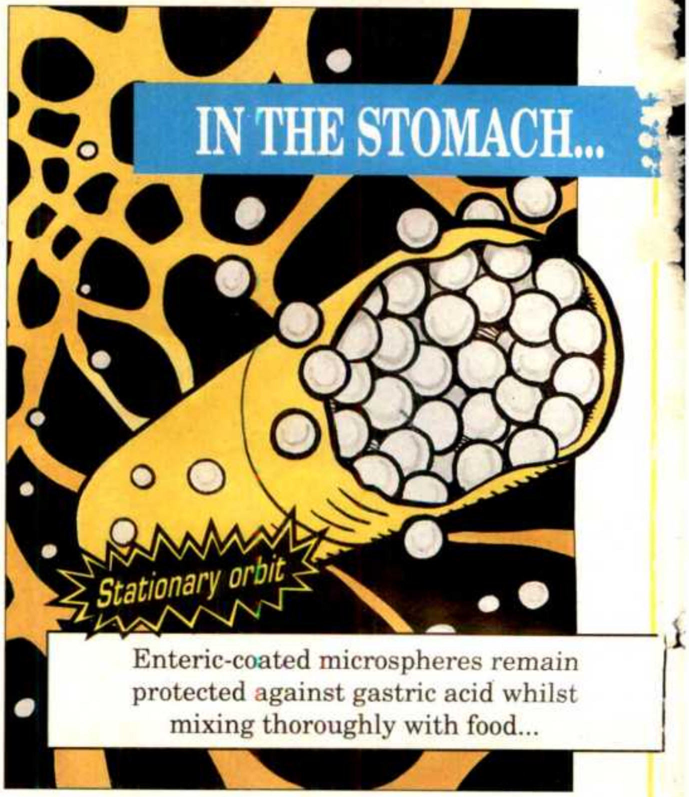
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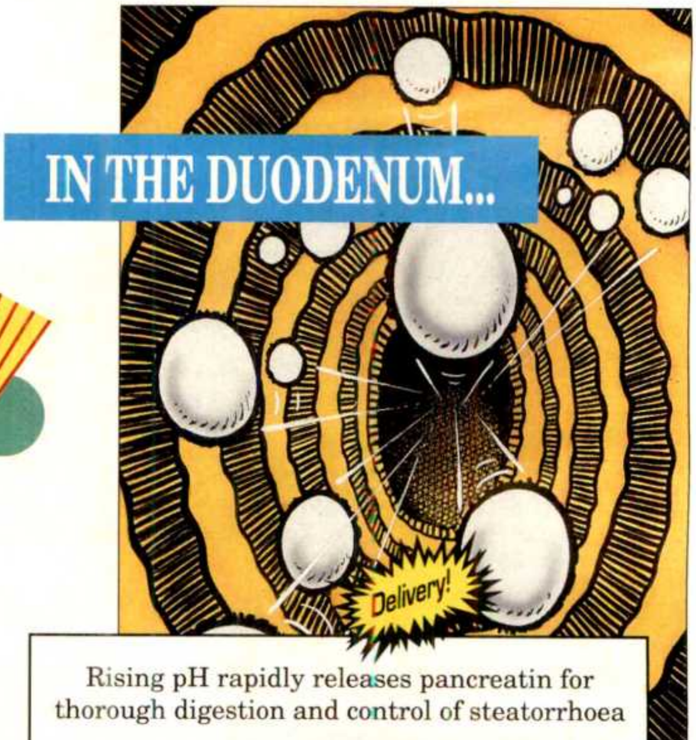
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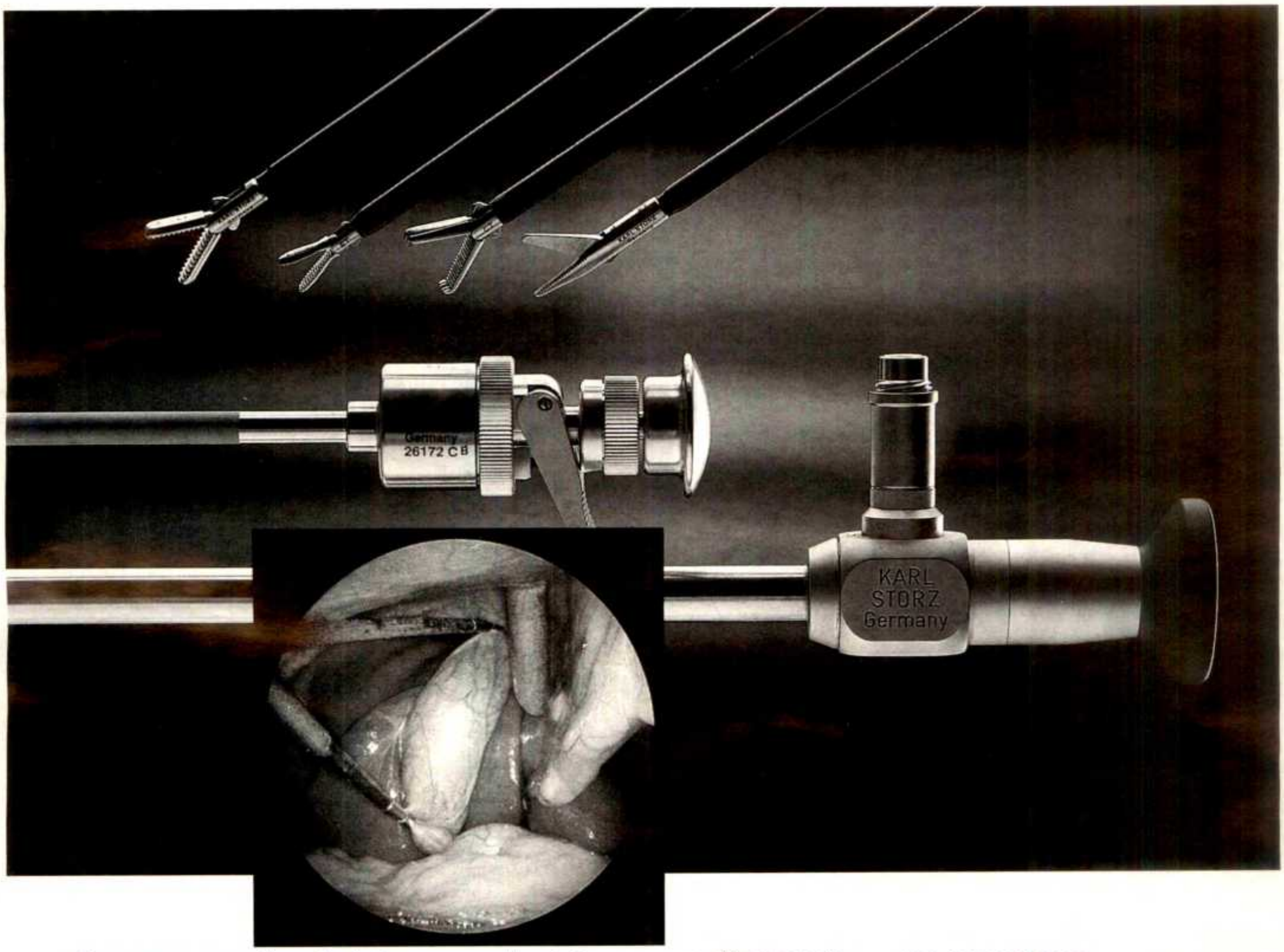

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Presentation: Single dose disposable syringes containing dalteparin sodium 2,500 IU (anti-Factor Xa)/0.2 ml or 5,000 IU (anti-Factor Xa)/0.2 ml. No preservative present. **Indication:** Peri- and post-operative surgical thromboprophylaxis. **Dosage:** Adults only. Moderate risk of thrombosis. Fragmin 2,500 IU administered subcutaneously (sc) 1—2 hours prior to surgery and thereafter 2,500 IU sc once-daily for five days or until the patient is fully ambulant. High risk of thrombosis eg elective hip replacement, extensive operations, patients with malignant disease. Fragmin 2,500 IU administered sc 1—2 hours prior to surgery, and the same dose is administered 12 hours later. Thereafter 5,000 IU sc once-daily for five days or until the patient is fully ambulant. **Contraindications:** There are no known absolute contraindications to Fragmin. However, caution should be exercised in patients with an increased risk of bleeding complications. **Precautions:** Caution in patients with severely disturbed hepatic or renal function, thrombocytopenia, or defective platelet function and in patients receiving drugs affecting coagulation/platelet function; patients with known heparin hypersensitivity. Fragmin, when administered in doses of 2,500—5,000 IU/day, does not generally accumulate and, therefore, monitoring of anti-Factor Xa levels is not usually necessary. **Side effects:** High doses of Fragmin with serum anti-Factor Xa levels greater than 1.5 IU/ml may cause bleeding. Transient slight to moderate increase in liver enzymes have been observed. The following heparin side effects cannot be excluded as Fragmin is a derivative of heparin: thrombocytopenia, allergic reactions, osteoporosis. **Overdose:** 100 IU Fragmin is inhibited by 1 mg protamine: see data sheet for full prescribing information. **Legal Category:** POM. **Packs:** Fragmin 2,500 IU/0.2 ml; pack of 10 single dose syringes. 5,000 IU/0.2 ml: pack of 10 single dose syringes. **P L Numbers:** 2,500 IU/0.2 ml 0022/0076. 5,000 IU/0.2 ml 0022/0077. **Kabi Pharmacia Ltd, Davy Avenue, Knowlhill, Milton Keynes, MK5 8PH.**

References: **1.** Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. **2.** Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. **3.** Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weight heparin given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. **4.** Eriksson B I, Kälebo P, Anthmyr B O et al. Prevention of Deep-Vein Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

Further information is available from: **Kabi Pharmacia Cardiovascular, S-112 87 Stockholm, Sweden.**

Eurosurgery 93

The Editors once again welcome Eurosurgery to our pages, in the publication this month of a supplement containing abstracts of papers presented at the Eurosurgery 93 meeting in London. This 3rd European Congress of Surgery unites specialists from all surgical disciplines in a single forum to discuss matters of common interest such as training in surgery, specialization, new techniques and research, as well as practical aspects of their own specialty. Once again, the quality and diversity of the abstracts included in the supplement speak for the excellence and variety of European surgery and its associated research activities.

Papers from Eurosurgery 92 were published in a special issue of the Journal in March 1993. The Editors hope that once again contributors to Eurosurgery 93 will give *The British Journal of Surgery* the opportunity to publish their work. Authors who wish to submit a paper may do so at the meeting, or directly to the Journal office (please note our new address) before the end of September. We hope that the papers selected for publication will appear in the Journal in the Spring of next year.

The Editors wish every success to Eurosurgery 93.

R. C. N. Williamson
J. R. Farndon
J. A. Murie
C. D. Johnson

Overseas Members of the Editorial Board

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September, 1090–1091

Further Board Members from around the world.

DR HENRY PITT
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Henry Pitt (born 1945) is Professor and Vice-Chairman, Department of Surgery, the Johns Hopkins Medical Institution, Baltimore, Maryland. He went to medical school at Cornell University, did his surgical training at Johns Hopkins and worked in Los Angeles before returning to the East coast. He has been Secretary of the Society of University Surgeons and of the Society of Clinical Surgery. He is well known for his work on biliary sepsis, obstructive jaundice and pancreatectomy.

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PROFESSOR ROLLAND PARC
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Rolland François Parc (born 1940) is Clinical Professor and Chairman of the Department of Gastrointestinal Surgery at Saint-Antoine Hospital, University Paris VI. His medical education and surgical training took place in the hospitals of Paris. He is Associate Editor of *Annales de Chirurgie* and *Hepatogastroenterology*. His particular clinical interest is in colorectal surgery, and he has just been elected an Honorary Fellow of The Royal College of Surgeons of England.

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PROFESSOR ANGELITA HABR-GAMA
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Angelita Habr-Gama is Professor of Surgery and head of the Colorectal Surgery Unit at the Hospital das Clinicas of the School of Medicine of the University of São Paulo. She qualified as a doctor at the University of São Paulo. Her special interest is colorectal surgery, particularly sphincter-saving operations for the treatment of rectal cancer. She was elected President of the Brazilian Society of Coloproctology in 1981 and is President of the Latin American Association of Coloproctology. She is also Vice-President of the Brazilian College of Surgeons.

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DR LUIS DA MOTA CAPITAO
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Luis A. L. da Mota Capitao was born in 1950. He graduated and did his surgical training in Lisbon apart from a year in the Vascular Surgical Unit at St Mary's Hospital, London. In 1990 he was appointed consultant surgeon at St Marta Hospital, Lisbon, and he is responsible for the Vascular Surgical Unit at S. Jose Hospital in that city. Within vascular surgery his main interests lie in aortoiliac and femorodistal bypass, critical ischaemia and carotid pathology.

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Robin Williamson

Br. J. Surg. 1993, Vol. 80, September, 1092–1093

Genetic testing for multiple endocrine neoplasia

In recent years it has been recognized that the neoplastic transformation of a somatic cell results from a defect, or combination of defects, at the genetic level. The study of certain familial diseases, such as the multiple endocrine neoplasia (MEN) syndromes, has identified specific chromosomal loci that appear to be pivotal in the development, not only of the inherited tumours, but of their sporadic counterparts as well.

Virtually all patients with MEN type 1 have parathyroid hyperplasia at the time of diagnosis; less than half have pancreatic islet cell tumours (usually gastrinomas) and less than one-quarter have pituitary tumours (usually prolactinomas). Occasionally these patients also develop adenomas of the thyroid gland or adrenal cortex. The MEN 1 gene has been assigned to a specific segment on the proximal long arm of chromosome 11 by genetic mapping[1], but to date the nature of this gene and the specific mutation(s) responsible for the syndrome have not been defined. Using molecular genetic techniques one can demonstrate, in DNA from both parathyroid and pancreatic islet cell tumours, allelic deletion of the portion of chromosome 11 harbouring the MEN 1 locus[1]. Furthermore, the deletion always affects the chromosome derived from the unaffected parent, thus allowing expression of the germline mutation that is inherited on the chromosome from the affected parent. This pattern is consistent with a 'two-hit' model of tumorigenesis, which involves mutation or loss of both homologues of the putative MEN 1 tumour suppressor gene. Although the MEN 1 mutation remains undiscovered, highly accurate DNA-based genetic testing[2] is possible based on the inheritance pattern of certain genetic markers situated very close to the position of the MEN 1 gene on chromosome 11. The clinical role of early genetic diagnosis of MEN 1 gene carriers is not clear, however, because surgical treatment for parathyroid hyperplasia, pancreatic islet cell neoplasia or pituitary neoplasia should not be undertaken until a clinical and biochemical diagnosis of the specific endocrine tumour has been established.

Virtually all patients with MEN 2A develop medullary thyroid carcinoma (MTC); approximately half will develop clinical or biochemical evidence of either phaeochromocytoma or parathyroid hyperplasia. Patients with the rare MEN 2B syndrome have MTC, phaeochromocytoma, mucosal neuroma and ganglioneuromatosis of the gastrointestinal tract. They also have a characteristic phenotype. Patients with familial MTC inherit only MTC and have none of the extrathyroid manifestations characteristic of MEN 2A or 2B.

Until recently, the standard for early diagnosis of MTC in patients at risk for MEN 2A was the measurement of plasma calcitonin levels by radioimmunoassay following stimulation with the calcitonin secretagogues calcium and pentagastrin[3]. The demonstration that the gene(s) for the distinct clinical syndromes MEN 2A, MEN 2B and familial MTC[4–7] each map to the centromere region of chromosome 10 was followed by the advent of DNA-based testing to identify individuals who have inherited the disease mutation before the time that they manifested either clinical or biochemical evidence of MTC[8,9].

Very recently, work in our own and other laboratories[10,11] has identified germline mutations in the *RET* proto-oncogene, a tyrosine kinase receptor gene on chromosome 10. These mutations are associated with the MEN 2A and familial MTC syndromes. Mulligan and co-workers[10] identified missense mutations in 20 of 23 apparently distinct families with MEN 2A. Similarly, Donis-Keller and colleagues[11] identified 12 different mutations in the germline DNA and tumour DNA from patients with MEN 2A and familial MTC. Each of the mutations described in these studies involves a codon for a highly conserved cysteine residue within the extracellular domain of the *RET* proto-oncogene tyrosine kinase receptor. This results in an amino acid substitution that presumably adversely affects the structure of the extracellular receptor portion of the molecule. The precise function and the ligand of the protein

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Professor Wells gave the Peter Heimann Lecture on this subject to the International Association of Endocrine Surgeons in Hong Kong, August 1993

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encoded by the *RET* proto-oncogene are not currently known. More importantly, the reason for the tissue specificity of neoplasia resulting from this germline mutation, which is present in every cell in the body, has not been elucidated. In contrast to MEN 1, there is no evidence of consistent allelic deletion of *RET* in the DNA from either the MTCs or phaeochromocytomas that develop in these patients. Patients with MEN 2A have been found to be heterozygous (i.e. retain one normal allele) for *RET* missense mutations in both germline *and* tumour DNA. If the mutations described cause the MEN 2A syndrome, then *RET* apparently acts as a dominant oncogene in the development of neoplasia in tissues derived from the neural crest.

It is interesting to note that mutations resulting in amino acid changes in the same cysteine codon are apparently responsible for the distinct clinical syndromes of MEN 2A and familial MTC. It has been postulated that other genes could modify the spectrum of expression or age of onset in different families. Although it seems likely that defects in the *RET* proto-oncogene are also responsible for the MEN 2B syndrome, mutations have not been found to date in the exons involved in MEN 2A or familial MTC. The possibility that a mutation in a contiguous gene results in the MEN 2B syndrome cannot be excluded. Finally, in the combined reports above six families with MEN 2A have been studied in which the mutations have not been detected and presumably lie within other exons not yet examined. The eventual detection of all the mutations within *RET* that would predict disease, and the implementation of an efficient means of making a genetic diagnosis, will almost certainly introduce important new issues in the management of family members at risk of these disorders.

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Br. J. Surg. 1993, Vol. 80, September, 1094–1096

Diathermy in laparoscopic surgery

The safety of monopolar radiofrequency electrical energy has been proven by 50 years of use during laparotomy. But how much do we know about diathermy and does its use differ in laparoscopic surgery?

Alternating current, the type used for surgical diathermy, is characterized by power output (the rate of power delivered at a given time) and frequency modulation. The latter refers to the number of changes in the direction of the current within 1 s and how this number changes over time. Empirically, it has been found that certain frequencies are more appropriate when cutting or coagulation is desired.

'Polarity' (monopolar *versus* bipolar) refers to the number of electrical poles at the site of application; the main difference is the distance between the poles. For monopolar, the second pole is the dispersive electrode plate, usually attached to the patient's thigh. In bipolar mode, the distance between the poles is a few millimetres and the current affects only the tissue located between these poles. Relatively low power is needed in bipolar mode; up to ten times more is required in monopolar mode because the body is a poor electrical conductor. The relatively low power of bipolar diathermy is insufficient to obtain the power density required to cut tissue. This power density is the key element that determines the thermodynamic effect. In general, a highly concentrated electrical field leads to vaporization (cutting) of tissue and a more dispersed field results in coagulation. It is possible to manipulate this bioeffect of electrical current only in the monopolar mode, although recent advances in bipolar technology may have overcome this problem[1]. Changing between, or combining, cutting and coagulation is usually achieved via a switch on the diathermy machine, but the surgeon may change the contact area at the point of dissection to convert a high-power 'cutting' output to 'coagulation' by holding, for example, a forceps between diathermy instrument and tissue, thereby reducing the power density.

Monopolar electrical energy is the most frequently used method of dissection in laparoscopic surgery today. Lasers have been readily adapted to laparoscopic surgery but have no proven safety benefit over the less expensive and more freely available electrocautery systems[2]. Laser dissection methods rely on the ability of light energy to excite molecules sufficient to cause heating of the recipient tissue and disruption of structural proteins[3]. Carbon dioxide laser dissection, in particular, has an inherent 'backstop effect' that is difficult to control and may lead to inadvertent damage of structures adjacent to the area of intended coagulation[4]. Newer technology using the neodymium yttrium–aluminium–garnet laser with contact tips has eliminated the danger of a free beam loose in a body cavity, but energy penetrates deeply (3–4 mm) and may injure adjacent tissue inadvertently.

The potential problems associated with the laparoscopic use of monopolar electrocoagulation are not fully appreciated[5]. They relate to unrecognized energy transfer ('stray current') outside the view of the laparoscope. During laparoscopic surgery electrical energy is passed through the abdominal wall via cannulas (which themselves may or may not be conductors) by instruments (which may or may not be adequately insulated) to tissues being dissected. The only part of this circuit that is visible is the tissue being dissected. Potential areas for concern include insulation breaks, induced currents between a correctly insulated instrument and its surrounding cannula (capacitative coupling), unintended contact with other metal instruments within the abdomen (direct coupling), energy transfer through tissue from the point of dissection, and arcing (sparking) to local structures from a dissecting electrode that has been activated but is not in contact with the body. Therefore, electrical injury remote from the site of surgery may occur as a result of tissue conduction, discharge of induced capacitative coupled current, and high-voltage sparking. Hunter[1], and Voyles and Tucker[5] recently addressed the problems of stray current outside the view of the laparoscope.

Insulation defects, although frequently not visually perceptible, may lead to near 100 per cent delivery of electrical energy at a site beyond the view of the laparoscope. The hazard of insulation failure depends on the location of the point of failure along the instrument. If in the handle, it may cause a shock to the surgeon. If outside the view of the camera, thermal injury may occur to any viscus in contact with the defective instrument. If it occurs within the metal cannula, the only evidence may be interference with the electrosurgical generator, jerking of the abdominal wall, or interference with the video monitor. This may be harmless as the current is dissipated

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by broad contact at the abdominal wall. If, however, the defective instrument is within a plastic cannula, there may be no clue to insulation failure. It is important that single-use instruments are not resterilized as this can lead to insulation breaks and inadvertent direct coupling.

Capacitative coupling can lead to laparoscopic complications, although the likelihood is remote. Current is induced in the metal cannula through which the dissecting instrument passes and may be transmitted to tissue outside the view of the laparoscope. Current is greater if 5-mm rather than larger diameter cannulas are used and if they are covered by a plastic tissue anchor. In the latter situation the cannula is isolated from the abdominal wall, preventing electrical dissipation through the dispersive electrode.

Electrical energy dissipated through tissue has the ability to cause distant necrosis that may become apparent only some time after surgery. The temperature generated by an electrical current is inversely proportional to the fourth power of the diameter of the body along which it is conducted. Structures of small diameter are, therefore, at risk of necrosis and subsequent perforation or stricture if they are in the line of current dispersion. For example, if the diameter of the appendix base is reduced by half with a ligature and the structure then divided using diathermy, the current density at the ligature will be four times greater than at the point of contact and the temperature increase will be 16 times greater, which may result in necrosis and perforation[1].

Arcing occurs when a high-voltage current jumps the distance between the electrode and nearest body tissue. This sparking discharge may occur if the electrode is left active but not in contact with the point of dissection and is proportional to voltage. The diathermy peak-to-peak potential difference should be less than 1200 V. Although considerable variation exists, diathermy machines that are more than 5 years old may be able to generate a peak-to-peak potential difference of 6000 V. Such a discharge can produce necrosis at the contact point of the spark.

In addition to the hazards of electrical current in diathermy dissection, the tip of an activated electrode generates substantial heat energy. If the active electrode is not in contact with tissue, a temperature of over 500°C can be generated, as the heat cannot be rapidly dissipated. If it touches a viscus, a thermal burn may result even after the diathermy has been made inactive[6]. If monopolar electrocoagulation is to continue as the preferred mode of dissection in laparoscopic surgery it is essential that surgeons understand its method of action and potential pitfalls.

What of non-laser alternatives to monopolar dissection? High-frequency ultrasonic coagulation[7] holds considerable promise as a cutting and coagulating energy source adapted for laparoscopic use. A piezoelectric transducer is housed in a handpiece causing a blade tip to vibrate at 55 kHz with a 50-μm excursion. The mechanical energy causes cutting and coagulation by vibrational forces; this cavitational effect vaporizes intracellular water and disrupts cell walls. Maximum blade temperatures do not exceed 80°C and the spread of necrosis from the point of contact (in the epidermis) is less than 0·05 mm, compared with 0·35 mm for electrothermal necrosis[8]. The technique of water-jet dissection has been used in hepatobiliary surgery selectively to dissect liver parenchyma while leaving vessels and ducts intact for subsequent ligation or coagulation. High- and low-pressure systems exist that deliver a jet of water of between 0·06 and 0·25 mm in diameter at 15–50 and 200–1000 bar (1500–5000 kPa and 20 000–100 000 kPa) respectively. Tissue penetration is decreased by increasing the distance between the jet nozzle and dissection area until the stream velocity is insufficient for cutting[9]. These innovative techniques promise an exciting future but they are not yet fully refined for laparoscopic surgery. It is possible that electrosurgery will be replaced by these methods but, until then, didactic lectures in monopolar electrocoagulation should be an integral part of training programmes in laparoscopic surgery.

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Announcement

European Surgical Fellowships

The Council of *The British Journal of Surgery* is pleased to announce the availability of European Surgical Fellowships for 1994. Last year four Fellowships were awarded, to Dr Jose Luis Aguayo-Albasini (Spain), Mr R. M. Charnley (Nottingham), Mr S. D. Heys (Aberdeen) and Mr T. G. John (Edinburgh).

It is Council's intention to offer European Surgical Fellowships again in 1994. Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the UK to visit centres in other European countries or surgeons working in other European countries to visit the UK. Applicants must be under 40 years of age and should submit details of their proposed itinerary and its anticipated cost, together with a copy of their *curriculum vitae* and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, by 1 February 1994.

D. C. Carter

Review

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Silicone gel breast implants, breast cancer and connective tissue disorders

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Recent worldwide media speculation that silicone gel-filled breast implants may be linked to an increased incidence of breast and other cancers, and connective tissue disease (particularly systemic sclerosis) has caused concern to the medical profession and public alike. Until carefully controlled studies have been performed to prove the safety of these implants, the US Food and Drug Administration has restricted their use to research and breast reconstruction. Research has so far failed to prove a causative relationship between silicone implants and cancer or connective tissue disorders.

The recent widespread media speculation that silicone implants may be linked to breast and other cancers, and to connective tissue disease – particularly systemic sclerosis – has highlighted a current cause for anxiety to both the medical profession and the public.

Surgical implantation of plastic materials for reconstruction or augmentation of the breast has become popular following the development in 1963 of the modern silicone implant[1]. Before the use of implants, developmental abnormalities of the breast were corrected by less satisfactory means using transplanted fat tissue, implantation of other synthetic materials such as polyvinyl alcohol, or injection of silicone or paraffin.

At least 2 million women in the USA now have silicone gel-filled implants. These are used for reconstruction following mastectomy for breast cancer, or to enlarge or reshape the breast for cosmetic purposes. The psychological benefits of these procedures are well recognized[2–4].

Silicones have never been found in nature, although they are derived from quartz or silica (SiO_2). They can be synthesized as viscous fluids, watery liquids, compounds, resins and rubber-like products[5]. Silicon is an abundant element in nature, foods and man-made products. It comprises 27 per cent of the Earth's crust; only oxygen, at 48 per cent, is more abundant. Large amounts of silicon are ingested in drinking water and it is an essential element for plants and probably also for mammals, including humans[6].

Silicone is composed of long chains of dimethylsiloxy groups; the longer the chain, the more viscous the fluid[5]. It is one of the least inflammatory of implanted alloplastic biomaterials[7]. The relative stability, non-reactivity and hydrophobic qualities of silicone in tissues proved valuable for many uses, ranging from lubrication of needles and syringes to coating of implantable devices such as penile implants, hip-joint prostheses and finger-joint prostheses. It has proved useful in an almost infinite range of physical forms, from oils and gels to soft and firm rubbers.

Silicone breast implants consist of a silicone elastomer shell that may be filled with a silicone gel by the manufacturer or with saline by the surgeon at the time of implantation (*Figures 1* and *2*). The silicone shell contains silica as a filler necessary for strength; silica is not present in the gel. In tissues, silica can cause silicosis, but whether it is released into the surrounding tissue from the prosthetic shell is not known[8].

The silicone elastomer is a semipermeable membrane and as such allows the gel to pass from the implant into the surrounding tissue by diffusion. This is known as 'bleed' and has been observed by many researchers[9–11]. Implant bleed can be seen by placing a gel-filled prosthesis on a paper towel: in just a few hours a sticky oily stain can be seen. Wickham *et al.*[12] used scanning electron microscopy to prove that the droplets in fibrous capsule biopsies contained silicone. Rudolph *et al.*[8] demonstrated that such droplets occur only around gel-filled implants, suggesting that the silicone came from the gel and not from the surrounding capsule. However, the presence of these droplets did not correlate with the clinical findings of a firm breast[8,13]. Silicone has also been noted in the surrounding capsule when saline-filled implants were used, but to a lesser extent[14]. It has also been found in sites distant

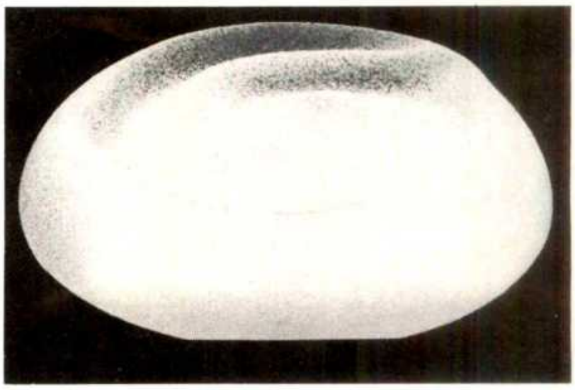

Figure 1 *Textured silicone gel-filled breast implant*

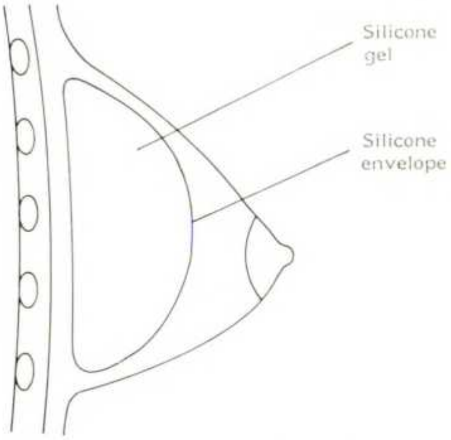

Figure 2 *Cross-section of the chest wall showing a breast implant* in situ

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from the implant such as the antecubital fossa[15], upper arm[16,17], chest and shoulder[17], and abdominal wall as far as the groin[18]. Rupture of the implant was evident in all these cases.

The surrounding tissue generally reacts with a mild transitory inflammatory response, without evidence of the chronic inflammation associated with toxicity or the antibody formation and plasma cell infiltration associated with an immune response. The tissue reaction is characterized from the first to third days by an infiltration of neutrophils, a few plasma cells and macrophages. By days 6–7 the number of leucocytes is significantly decreased and a band of fibroblasts surrounds the silicone. A fibrous capsule progressively develops over the next 2–3 weeks. The deposition of this relatively acellular layer of connective tissue has been described as the normal wound-healing response to a large inert foreign body in a sterile environment[19]. Breast implants always produce a surrounding fibrous capsule, following which there is little tissue reaction[20]. This inflammatory response is often associated with a degree of capsular contraction that in almost 10 per cent of cases causes sufficient discomfort and distortion of the breast to require secondary surgery. Myofibroblasts have been detected within the capsule and may be the cause of the contracture[8]. If the implant ruptures, the capsule is found to be thicker[21].

Capsular contraction is the most frequent complication of breast augmentation[22,23]. With the original smooth-walled implants there was a 30–50 per cent incidence of significant contracture[24–26]; textured implants cause less capsular contraction than smooth-walled prostheses[25,27,28]. A similar improvement was seen with the use of polyurethane-coated implants[29–31] but these have been withdrawn from the market after allegations that they are carcinogenic because of the breakdown of the polyurethane coating to 2,4-toluene diamine. Capsular contraction is found when saline-filled implants are used but to a lesser extent than that associated with silicone gell-filled prostheses[32]. The newer low-bleed implants show a lower contracture rate than conventional devices[33].

Recommended methods of preventing contracture include atraumatic technique[34,35], areolar incision[36,37], submuscular placement of the prosthesis[37], wide surgical pocket[35,38], double-lumen prosthesis[39], local cortisone[39,40], routine administration of antibiotics[40–42], vitamin E[43], and rapid and late mobilization[23,40] by bandage or massage of the implant. While there is no way of avoiding this complication completely, the newer low-bleed textured gel implants seem to have reduced the incidence of capsular contracture to a useful degree.

Carcinogenicity

In 1953, Oppenheimer *et al.*[44] reported the development of sarcoma in Wistar, Sherman, Longacre, Paris and C57 strains of rat after plastic had been embedded. In 1955, silicone was added to the list of solid materials presumed to be the stimulus for sarcoma development[45]. Rats are known to be highly susceptible to sarcoma following exposure to carcinogens, but such tumours have not been induced in higher mammals[46,47]. At no time during these or any subsequent study has an increase in the incidence of breast adenocarcinoma attributable to silicone been observed.

A large number of women have now been exposed to silicone implants and any question of carcinogenicity must be viewed against the normal background of cancer in humans. The incidence of breast cancer in women is 1:10 in the USA and 1:12 in the UK[48]. Breast cancer has been reported in women with implants[1,46,47,49,50] but, as yet, there is no evidence that prostheses cause cancer or that breast cancer occurs with a greater frequency among women receiving augmentation than in the general population[51–53].

Two studies in the USA have suggested that the incidence of breast cancer is less in patients with implants[54,55]. In these studies, cancer registration data were used to ascertain breast cancer outcomes and to estimate breast cancer rates in the background population. Both studies found a lower than expected incidence of breast cancer in women with implants (relative risk 0·5 and 0·7 respectively), although in neither was this statistically significant. The study by Deapen and Brody[55] reported significantly higher incidences of lung (relative risk 2·1) and vulval (relative risk 5·3) cancer, although these arose in a survey of a range of cancer sites. These studies depended on the accuracy of linkage with a subnational cancer registry to determine outcomes. Bias may be introduced by, for example, unusual socioeconomic characteristics of the patients given augmentation relative to the background population; it could be that the former are more mobile and therefore more likely to move out of the study ascertainment area. This could be avoided in a matched cohort study in which both cases and controls are equally likely to be lost to follow-up, but no matched cohort or case–control study has been published.

Silverstein *et al.*[56] compared 20 previously augmented patients with breast cancer with 248 non-augmented controls with breast cancer. All 20 were cases of invasive tumour and the relative risk for nodal involvement at presentation was 1·9 for women with implants compared with those without augmentation. This apparent tendency for breast tumours to be detected later in cases than in controls is not consistent with earlier reports[1] from Deapen's cohort, in which the patients with breast cancer tended to have disease at an earlier stage at the time of diagnosis. The evidence to date suggests that implants are not a risk factor for breast cancer and that the survival rate among these women with cancer is no lower than expected.

Connective tissue disorders

Systemic sclerosis is an immune-mediated disorder of connective tissue characterized by overproduction of collagen leading to sclerotic changes in the skin and visceral organs. Typical of the disease are induration and thickening of the skin (scleroderma), Raynaud's phenomenon and other vascular abnormalities, musculoskeletal manifestations and visceral involvement, especially that of the gastrointestinal tract, lungs, heart and kidneys. In addition to systemic sclerosis, systemic lupus erythematosus, polymyositis, dermatomyositis, Raynaud's syndrome and rheumatoid arthritis have all been described in association with silicone implants. However, little is known about the aetiology of these diseases and associations include exposure to toxic oils, vinyl chloride, other solvents and resins, and silica among miners as well as augmentation mammoplasty. The incidence of systemic sclerosis in the general population[57–64] varies in different studies from 0·6 to 20 cases per million per year. The most recent report, a 20-year incidence study, found a mean annual incidence over the decade to 1982 of just under 20 cases per million population[64]. Systemic sclerosis is at least three times more common in women than men[57,64]. The prevalence of scleroderma is thought to be about 25 per 100 000 female population[65].

Connective tissue disorders have been reported to occur following cosmetic surgery (including breast augmentation) employing injection of foreign substances such as paraffin and silicone[66,67]. A great deal of alarm was caused recently by claims in the lay media that systemic sclerosis in particular, or connective tissue disease in general, may be caused by exposure to the silicone-containing implants used for breast augmentation or reconstruction. The suspicion of an association between autoimmune disease and silicone gel-filled breast implants has arisen from over 100 case reports; these have led some to believe that silicone might serve an 'adjuvant' role in the development of autoimmune disease. Much of this literature comes from Japan and, while the majority of cases resulted from injection of material such as paraffin or silicone of unknown origin and composition, there have been instances in which implants have been implicated[23,68–75]. A recent study in the USA found that patients with a defined autoimmune disorder and a silicone breast implant had high titres of antinuclear antibodies, and that the specificities of these antibodies were similar to those found in the idiopathic form of the relevant autoimmune disease. Trauma with resultant rupture of the prosthesis seems to accelerate the onset of symptoms and systemic sclerosis is the commonest disorder among patients with breast implants[76].

Despite many case reports in the literature, few epidemiological studies have been conducted. The risk of systemic sclerosis in women receiving implants for breast augmentation has been estimated in two reviews of case reports. However, Kondo *et al.*[77] and Shons and Schubert[78] presented grossly different estimates of the risk for augmented women relative to the background population: 3·0 and <0·1 respectively. This disparity is due in large part to different estimates of the background incidence of systemic sclerosis. Neither study attempted to use the conventional person-years of follow-up approach nor to calculate age-specific background rates. No properly controlled epidemiological study of systemic sclerosis in patients with augmentation or breast reconstruction has been published.

An independent advisory committee on silicone gel-filled breast implants was set up in Canada in February 1992. This committee found that the reported cases of so-called autoimmune disease in women with implants are proportionately far less numerous than in women without implants. They concluded that there is an absence of evidence that women with implants are more likely than those without to have an autoimmune disorder and that more research is required[79]. Until carefully controlled studies have been performed to prove the safety of silicone prostheses, the US Food and Drug Administration has banned their use for purely cosmetic indications but permits implantation in women with breast cancer, congenital disorders or traumatic injury. Although research has so far failed to prove that silicone gel-filled breast implants cause connective tissue disorders or cancer, work must continue as a question mark still remains over their safety.

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Role of surgery in patients with primary non-Hodgkin's lymphoma of the stomach: an old problem revisited

The literature after 1980 dealing with the treatment of primary gastric non-Hodgkin's lymphoma (stages I and II) is reviewed. Gastrectomy is recommended for patients with acute symptoms at presentation or with complications of chemotherapy or radiotherapy. In elective cases, patients with stage I disease may be candidates for gastrectomy as a single therapy, provided that tumour-free resection margins are achieved. There is no evidence of substantial benefit from adding postoperative chemotherapy or radiotherapy after an apparently radical resection. In stage II disease, the best results are achieved with ablative surgery plus adjuvant therapy. The resection volume should be limited to macroscopically involved structures, in principle avoiding total gastrectomy and extensive lymph node dissection, since residual disease may be optimally controlled with radiotherapy or chemotherapy. Primary chemotherapy, with or without radiotherapy, represents an experimental approach; the advantages of sparing the stomach must be balanced against the toxicity of an aggressive chemotherapy regimen and the risk of emergency operation for iatrogenic complications.

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Primary gastric lymphoma has long accounted for only 1–7 per cent of all malignancies of the stomach, but recent studies[1–4] indicate that its incidence is increasing. A recent report from the Surveillance Epidemiology and End Results Committee[4], which evaluated approximately 13 per cent of the total population of the USA, found a twofold increase in the age-adjusted incidence limited to people over 60 years of age.

The stomach is the commonest site of primary extranodal lymphoma[5–19]; it is even more commonly involved in the dissemination of nodal lymphoma[14,20,21]. Approximately one-sixth of patients with systemic disease have gastric involvement[22,23], but this rate may reach 50 per cent if necropsy series are taken into account[24].

The need for a periodic review of the role of surgery in the diagnosis and treatment of primary gastric non-Hodgkin's lymphoma derives from three assumptions. First, because of the rarity of the disease it is difficult for a single institution to accumulate enough experience to determine the best treatment. Second, the development of imaging techniques such as computed tomography (CT), magnetic resonance imaging and ultrasonography has substantially curtailed the indication for laparotomy for staging (if not for diagnosing) the disease. Third, the encouraging results obtained by using cytotoxic drugs on advanced lymphoma have prompted some groups to propose primary chemotherapy, even for early stages of the disease when the lymphoma is confined to the stomach and when surgical results are generally good.

A critical appraisal of the literature is difficult because most reports are retrospective and hence inherently biased, and many publications deal with gastrointestinal lymphoma and include patients with different sites (stomach and small or large bowel) and different stages of disease. Moreover, clinical staging and especially histopathological classification have changed over the years. To minimize such difficulties, this review considers mainly data[1–100] published since 1980 and focuses on the role of surgery in patients with lymphoma confined to the stomach (stages IE and IIE).

Pathology

Primary gastric non-Hodgkin's lymphoma has recently been defined as a clinicopathologically distinct entity that differs from non-Hodgkin's lymphoma of peripheral lymph nodes both in its clinical behaviour[55] and in its morphology. Isaacson *et al.*[60] have suggested that such extranodal lymphoma arises from lymphoid tissue that may develop at extranodal sites during inflammatory diseases – mucosa-associated lymphoid tissue (MALT) – and that neoplastic cells follow the familiar pattern of their normal counterparts and remain localized at extranodal organs[56]. Most MALT-derived lymphomas are of B cell origin; the tumours are composed of so-called centrocyte-like cells, so named because of their resemblance to centrocytes[57]. These cells appear to derive from lymphoid cells normally found at the periphery of the follicles of Peyer's patches and selectively infiltrate the dome epithelium[58]. A distinctive feature of centrocyte-like cells is their tendency to invade the mucosal epithelium and form characteristic lymphoepithelial lesions, with penetration into the wall of the mucosal crypts and eventual disruption of the epithelial structure. Centrocyte-like cells show immunoglobulin light-chain restriction but not *bcl2* gene rearrangement or the CD22^{+} CD23^{-} CD5^{-} CDw32^{+} CD43^{+} phenotype.

Other components that contribute to the histology of MALT gastric lymphoma are plasma cells, and lymphoplasmacytoid cells and follicles. The latter tend to be near the muscularis mucosae and beneath the centrocyte-like cell infiltrate. These neoplastic follicles are not composed of follicle centre cells but result from colonization of reactive follicles by centrocyte-like cells[59].

Owing to its derivation from a separate lineage of B cells, gastric MALT lymphoma does not fit into any of the categories described in commonly used classifications and formulations. Isaacson *et al.*[60] proposed a list of principal categories of primary gastrointestinal lymphoma (*Table 1*). In the stomach, in addition to low-grade B cell lymphoma of the MALT type,

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Table 1 *Histopathological classification of primary gastrointestinal lymphoma*[60]

B cell
1. Low-grade B cell lymphoma of MALT
2. High-grade B cell lymphoma of MALT, with or without evidence of a low-grade component
3. Mediterranean lymphoma (immunoproliferative disease of the small intestine), low, mixed or high grade
4. Malignant lymphoma, centrocytic (lymphomatous polyposis)
5. Burkitt-like lymphoma
6. Other types of low- or high-grade lymphoma corresponding to peripheral lymph node equivalents

T cell
1. Enteropathy-associated T cell lymphoma
2. Other types unassociated with enteropathy

MALT, mucosa-associated lymphoid tissue

Table 2 *Staging systems for primary gastrointestinal non-Hodgkin's lymphoma*

Classification				
Ann Arbor[101]	Rao *et al.*[29]	Musshoff[102]	Description	Relative incidence (%)
IE	IE	IE	Tumour confined to gastrointestinal tract	26
IIE	IIE	IIE	Tumour with spread to regional lymph nodes	26
IIE	IIIE	IIE	Tumour with nodal involvement beyond regional lymph nodes (para-aortic, iliac)	17
IIIE–IV	IVE	IIIE–IV	Tumour with spread to other intra-abdominal organs (liver, spleen) or beyond abdomen (chest, bone marrow)	31

there are high-grade tumours composed mainly of centroblasts and in which there may be evidence of a low-grade residual component. Other types of non-Hodgkin's lymphoma corresponding to lymph node equivalents are rare.

Diagnosis and staging

A diagnosis of primary gastric lymphoma requires histological confirmation of a lymphoproliferative neoplasm in a clinical setting in which palpable adenopathy and hepatosplenomegaly are absent; there should be no evidence of lymphoma on chest radiography, CT, peripheral blood smear or bone marrow aspirate, and biopsy. The definition generally assumes the presence of symptoms referable to the upper gastrointestinal tract (abdominal pain, anorexia, nausea, vomiting), usually accompanied by an anatomically discernible lesion on double-contrast radiography or gastroscopy. Staging systems are shown in *Table 2*.

Contrast radiographic studies in patients with primary gastric lymphoma show various patterns, including a mass or filling defect in 71 per cent of cases. Ulcerative lesions are rare. A diffuse infiltrating process with thickened mucosal folds is seen in 20 per cent of cases[103–105]. These findings, while characteristic, are non-specific and often indistinguishable from other conditions such as gastric adenocarcinoma, Ménétrièr's disease, chronic gastritis and benign segmental hyper-rugosity. Because of this, a correct diagnosis of gastric lymphoma in the past has often required laparotomy. Early lesions may be mistaken for benign ulcers, and partial 'healing' of gastric lymphoma after H_2 antagonist therapy has been reported at endoscopy[44].

Recent evidence suggests that the accuracy of diagnosis by endoscopic biopsy is >90 per cent[63,64], but it is influenced by several factors. First, a lymphoma often grows in the submucosa and invades the mucosa only later in its course. Second, large ulcerating lesions may exfoliate necrotic material, which is difficult to interpret histologically. Third, when only small numbers of cells are available, a differential diagnosis between lymphoma and anaplastic carcinoma, or between small cell lymphoma and pseudolymphoma, is often impossible.

Since patients with proven gastric lymphoma are now subjected to an extensive diagnostic assessment that includes (besides careful clinical examination) CT of the lungs and abdomen, bone marrow aspirate and biopsy, and indirect laryngoscopy, it is unlikely that surgical exploration of the abdominal cavity would lead to a significant change in the staging of the disease. Staging laparotomy is, consequently, no longer recommended, even though the accuracy of CT in imaging regional gastric nodes is limited and may result in some understaging of patients[61,65]. However, if the surgeon embarks on a laparotomy because a preoperative histological diagnosis is lacking, diagnostic sampling of the liver, spleen, and mesenteric and retroperitoneal nodes is required in addition to gastric resection.

Emergency surgery at clinical presentation

Surgery may be required as an emergency procedure in patients with lesions that are obstructing, bleeding or perforated. *Table 3* describes the prevalence of features that might necessitate emergency surgery. The figures are somewhat biased because the criteria used to define bleeding and obstruction are not

Table 3 *Prevalence of bleeding, perforation and obstruction at clinical presentation in non-Hodgkin's gastric lymphoma*

Reference	Year	Bleeding (%)	Perforation (%)	Obstruction (%)
Contreary *et al.*[9]	1980	15	—	—
Herrmann *et al.*[14]	1980	36	—	—
Shiu *et al.*[23]	1982	29	—	—
Orlando *et al.*[31]	1982	30	8	—
Dworkin *et al.*[11]	1982	30	—	—
Fleming *et al.*[8]	1982	28	—	—
Brooks and Enterline[32]	1983	n.a.	3	n.a.
Mittal *et al.*[28]	1983	n.a.	5	n.a.
Shimm *et al.*[33]	1983	32	—	—
Gospodarowicz *et al.*[34]	1983	20	—	—
Paulson *et al.*[25]	1983	16	—	3
Thorling[35]	1984	25	—	2
Economopoulos *et al.*[36]	1985	17	—	—
Dragosics *et al.*[37]	1985	19	—	—
Skudder and Schwartz[38]	1985	43	—	7
Sheridan *et al.*[27]	1985	—	20*	4
Liang *et al.*[40]	1987	67	18	—
Taal *et al.*[41]	1987	6	—	—
Joensuu *et al.*[42]	1987	26	—	—
Hockey *et al.*[43]	1987	8·5	—	4·6
Adkins *et al.*[44]	1987	—	20	—
Jones *et al.*[39]	1988	7	—	4
List *et al.*[45]	1988	29	—	4
Bolognese *et al.*[46]	1988	9	—	—
Bron *et al.*[47]	1989	20	—	—
Shaw *et al.*[48]	1989	16	—	—
Bailey and Laws[49]	1989	42	—	—
Solidoro *et al.*[50]	1990	37	—	—
Jaser *et al.*[51]	1990	18	—	—
Gobbi *et al.*[52]	1990	2·6	—	1·3
Shutze and Halpern[53]	1991	33	—	40

n.a., Data not available. *All patients had disease of stage IV or were inoperable

Table 4 *Prevalence of emergency surgery after haemorrhage or perforation during therapy for non-Hodgkin's gastric lymphoma*

Reference	Year	No. of patients	Emergency surgery (%)	Type of therapy
Haemorrhage				
Rosenfelt and Rosenberg[54]	1980	27	26	Chemotherapy plus radiotherapy
Fleming *et al.*[8]	1982	15	60	CHOP
Mittal *et al.*[28]	1983	9	0	Radiotherapy
Economopoulos *et al.*[36]	1985	9	11	CHOP
Sheridan *et al.*[27]	1985	5	20	CHOP
Liang *et al.*[40]	1987	6	50	Chemotherapy
Burgers *et al.*[61]	1988	32	6	CHOP plus radiotherapy*
Bozzetti *et al.*[62]	1991	52	0	Chemotherapy plus radiotherapy
Perforation				
Fleming *et al.*[8]	1982	15	0	CHOP
Brooks and Enterline[32]	1983	3	0	Radiotherapy
Mittal *et al.*[28]	1983	9	0	Radiotherapy
Sheridan *et al.*[27]	1985	5	20	CHOP
Bozzetti *et al.*[62]	1991	52	2	Radiotherapy

CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone. *30 Gy

uniform in the literature, and tertiary referral centres for oncological therapy tend to underestimate the true prevalence of acute symptoms. The prevalence of bleeding in the literature is 20–30 per cent; lower rates of perforation and obstruction (occasionally higher values) have been reported[38,40,49,50]. Severe bleeding or perforation requiring immediate surgery occurred in 10 per cent of the present authors' patients with stage I or II lymphoma[62].

Subtotal gastric resection is preferable in patients requiring emergency operation. Simple suture of a perforated wall, even if patched with omentum, or simple ligation of the gastric vessels in bleeding lesions are procedures to be adopted only if the stomach cannot be resected. Proper healing cannot be expected in neoplastic tissue and further perforation is likely to occur as soon as radiotherapy or chemotherapy begins. Moreover, the abundant blood supply of the stomach makes ligation of the vascular pedicles of uncertain benefit. In patients with an obstruction of the stomach outlet, resection is preferred to simple gastrojejunostomy or catheter jejunostomy, since removal of the stomach may provide a cure and obviates the subsequent risk of bleeding and perforation during medical therapy.

Emergency surgery during chemotherapy or radiotherapy

Several authors, including both surgical and medical oncologists, have advocated early surgery, before chemotherapy or radiotherapy, to eliminate the risk of bleeding or perforation associated with the destruction of tumour tissue in the gastric wall[9,14,18,19,30,58,67]. Data on the prevalence of such complications in the literature of the past decade are summarized in *Table 4*. Haemorrhage is associated both with chemotherapy alone (usually cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), with or without bleomycin) and when combined with radiotherapy, with a prevalence between 11 and 20 per cent[27,68]. Perforation is reported after chemotherapy or radiotherapy in a variable proportion of patients, ranging from 0 to 10–20 per cent[27,68].

Risk factors for such complications have not been adequately elucidated. Perforation probably occurs more often when the entire thickness of the gastric wall is involved (a condition now well recognized by endoscopic ultrasonography)[41,69–71], whereas haemorrhage may be more likely in ulcerative lesions. Concurrent thrombocytopenia may make haemorrhage more frequent and more difficult to manage. The presence of leukopenia may similarly increase the operative risk in patients requiring emergency surgery. In the present authors' experience, the mortality rate for elective subtotal or total gastrectomy is 6–7 per cent, but one of two patients submitted to emergency operation died[62].

Table 5 *Survival rate at 5 years by stage after different treatments in non-Hodgkin's gastric lymphoma*

			Survival rate (%)	
Reference	Year	No. of patients	Stage IE	Stage IIE
Surgery				
Lim *et al.*[13]	1977	36	88	32
Herrmann *et al.*[14]	1980	10	60	40
Weingrad *et al.*[18]	1982	24	85	45
Paulson *et al.*[25]	1983	16	100	37
Maor *et al.*[26]	1984	12	67	40
Surgery plus radiotherapy				
Herrmann *et al.*[14]	1980	10	75	100
Shiu *et al.*[23]	1982	21	50	67
Weingrad *et al.*[18]	1982	32	83	62
Maor *et al.*[26]	1984	12	80	28
Surgery plus chemotherapy				
Paulson *et al.*[25]	1983	10	100	70
Maor *et al.*[26]	1984	5	100	20
Sheridan *et al.*[27]	1985	14	100	75
Surgery plus radiotherapy plus chemotherapy				
Maor *et al.*[26]	1984	13	60	62
Radiotherapy				
Weingrad *et al.*[18]	1984	9	85	
Paulson *et al.*[25]	1983	3		0
Mittal *et al.*[28]	1983	n.a.	67	55
Rao *et al.*[29]	1984	n.a.	100	78
Chemotherapy plus radiotherapy				
Mittal *et al.*[28]	1983	n.a.	100	75
Maor *et al.*[30]	1990	34*	79	73

n.a., Data not available. *Two later underwent partial gastrectomy

Surgery as a therapy

The results of surgery are shown in *Table 5*. These are somewhat biased because they do not include patients who have undergone simple laparotomy or bypass (the resectability rate ranges from 66 to 88 per cent[13,43,44]). It is therefore difficult to compare the surgical results with those of alternative treatments such as chemotherapy or radiotherapy. A common finding is that surgical resection alone is associated with a 5-year survival rate >80 per cent in the largest series of patients with stage IE disease. At this stage the prognosis is little affected by the addition of radiotherapy, but the addition of postoperative chemotherapy appears further to improve the results. However, caution is required before drawing definite conclusions because the combination of surgery, chemotherapy and radiotherapy gave poor results in the experience of Maor *et al.*[26]. Experience with radiotherapy or chemotherapy alone is very limited; results are no better and possibly worse than with surgery alone.

For patients with gastric lymphoma of stage IIE, the prognosis is improved by 50 per cent if surgery is followed by chemotherapy, radiotherapy or both. The 5-year survival rate of patients treated by surgery alone is about 40 per cent; this figure reaches 60–70 per cent in larger series in which radiotherapy[18,23] or chemotherapy[25,27] was combined with gastrectomy. As in patients with stage IE disease, the efficacy of non-surgical therapy is controversial; results of only a few studies are available.

It could be concluded, from analysis of the literature on stage IE gastric lymphoma, that ablative surgery – alone, combined with chemotherapy, or with chemotherapy plus radiotherapy – is the therapeutic approach most frequently associated with the best survival. This view is in keeping with the results of multivariate analyses of prognostic factors in four large series[72–75], two of which each involved over 100 patients[72,73]. These studies stressed the key role of resectional surgery and the unpredictable benefit of additional postoperative treatments.

Any suggestion of potential efficacy of primary chemotherapy with multiple drugs is indirect, coming from studies[50] of patients with stage III or IV disease in whom standard treatment (cyclophosphamide, vincristine and prednisone with or without bleomycin and/or procarbazine) achieved a complete response in 16 of 18 patients and a negative histological result in 90 per cent of those who underwent restaging. In the recent experience of Maor *et al.*[30] with 34 patients classified as stage IE or IIE given chemotherapy (CHOP plus bleomycin) alternated with radiotherapy (a mean of 3946 cGy), the 5-year survival rate was 73 per cent, the disease-free survival rate was 62 per cent, treatment-related deaths accounted for 6 per cent, and 15 per cent of patients experienced serious treatment-related morbidity. The natural history of gastric lymphoma, in which the common pattern of disease recurrence after surgery (with or without radiotherapy) involves distant sites[38,73], suggests that there is a need to include chemotherapy in all treatment protocols.

Surgical resection: how much?

'Local' radicality, i.e. the achievement of tumour-free margins at transection of the stomach, should be distinguished from 'regional' radicality, which means removal of regional lymph nodes and involved surrounding structures. Although some authors[23,76] have claimed a need for tumour-free resection margins, others have shown by univariate and multivariate analysis that patients whose surgical specimens had margins involved by tumour did not have a worse relapse-free survival than those with clear margins, provided radiotherapy was subsequently given[18,33]. Most authors[26,32,62,66] support the view that subtotal gastrectomy is the preferred procedure when feasible, even though lymphoma is multifocal in 14 per cent of cases[77]. Resection of the whole stomach adversely affects nutritional status and quality of life compared with subtotal gastrectomy[78]. Furthermore, deterioration in nutritional status may lead to poor compliance with further aggressive chemotherapy and so be associated with a poor outcome[79].

The importance of regional radicality in extragastric tissues has been stressed in many multivariate analyses[27,37,43,67,81,82], but the retrospective nature of such studies makes it uncertain whether the poor prognosis after non-radical resection indicates inadequate excision or simply reflects a more advanced stage of disease.

Conclusion

The first reported gastrectomy for lymphoma was performed 76 years ago in a 9-year-old child who was still disease-free 31 years later[44]. Nevertheless, the role of surgery in the treatment of gastric lymphoma is still debated. Whereas there is no doubt that surgery may be recommended when there is a strong suspicion of lymphoma but histological confirmation is lacking or in emergency conditions due to gastric bleeding or perforation, the necessity and timing of elective gastrectomy in patients with an established diagnosis and stage IE or IIE gastric lymphoma are controversial. For a proper comparison between surgery and chemotherapy or radiotherapy, not only oncological results but also morbidity and mortality rates resulting from therapy should be analysed.

The operative mortality rate for elective subtotal or total gastrectomy was about 3 per cent in the present authors' series[62] and <5 per cent in a survey of the literature[63] on patients operated on in the decade 1980–1990. Total gastrectomy is accompanied by nutritional sequelae[78] that may be clinically significant, particularly in elderly patients. However, such patients are also poor candidates for chemotherapy or radiotherapy.

In recent chemotherapy protocols[83–87], the rate of treatment-related death for nodal non-Hodgkin's lymphoma ranged from 1 to 10 per cent, depending on the aggressiveness of the regimen. Furthermore, there is evidence that acute non-lymphocytic leukaemia can occur as a dose-dependent treatment complication[88–91], as can carcinoma of the urinary bladder[92] and (more sporadically) Hodgkin's disease[93].

We maintain that elective gastrectomy, preferably subtotal, is required in patients with stage I gastric lymphoma. The oncological results of surgery alone are good and treatment-related mortality is limited. Adjuvant treatments have no proven value but, if deemed desirable, they may be administered safely without the related risks of iatrogenic bleeding and perforation. However, it is questionable whether it is possible to identify patients successfully at this initial stage.

With progressive advances in technology and expertise, endoscopists have recently succeeded in detecting 'early lymphoma' as a lymphoma limited in its depth of infiltration to the mucosa and submucosa[94–96]. It is noteworthy that the incidence of early gastric lymphoma among non-Hodgkin's lymphomas of the stomach ranges from 21·7 per cent in German-speaking countries[37] before 1988, to 47·9 per cent in the recent experience of Stolte and Eidt[80], to 45·9 per cent[97] in the Japanese literature. Moreover, such studies found a correlation between limited infiltration of the lymphoma and both a low degree of malignancy[80,98,99] and a low rate of involvement of perigastric lymph nodes[80,97]. The advent of endoscopic ultrasonography[69,71] also seems to have promise for accurate preoperative staging of the disease. Adequate preoperative staging of the lymphoma should therefore enable the oncologist to define the prognostic factors (stage IE, size <7 cm, no involvement of the serosa) that determine a successful outcome following surgery alone[32].

For patients with stage IIE disease, some authors[22,26,52] advocate primary chemotherapy with or without radiotherapy, which could be followed by gastrectomy in non-responders. Although this approach, which has not yet been validated by controlled studies, is interesting, it should be realized that surgery in patients receiving chemotherapy or radiotherapy carries an operative risk higher than that in untreated patients.

Finally, the present mortality rate after elective subtotal or total gastrectomy is 2–3 per cent in European studies, including the present authors' own[106], but it may increase fivefold to tenfold in an emergency setting. Balancing the risk of early surgery against surgery following medical therapy implies maintaining the prevalence of iatrogenic haemorrhage or rupture at a rate of 0·2–0·6 per cent, a value much lower than that reported in the literature.

It is imperative that future cooperative studies aimed at determining the optimal therapeutic approach should consider, besides stage of disease, other traditional and new prognostic indicators, such as nodular pattern and low nuclear grade *versus* diffuse and high-grade patterns[39,100,107], and levels of Ki67, a nuclear marker of tumour proliferation[108]. This will be possible only if patients are enrolled in prospective multicentre protocols.

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Idiopathic slow-transit constipation

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Until recently, the surgical management of idiopathic slow-transit constipation had remained unchanged since the condition was first described by Arbuthnot Lane in 1908. Although colectomy and ileorectal anastomosis is a successful treatment for the majority of patients, symptoms persist or are worse in some cases following such surgery. The previously inaccessible colon is now an area of interest in both health and disease; recent observations on aetiology, clinical investigation, neuropathology and surgical outcome lead us to question the rationale of colectomy for all patients with severe constipation.

At the beginning of this century Arbuthnot Lane[1–4] reported in a series of communications to the *British Medical Journal* the results of colectomy and ileorectal anastomosis for severe constipation. He identified a group of patients, predominantly women of child-bearing age or younger, with severe constipation whose symptoms could be improved dramatically by removal of the colon. He also observed that the colon of these women, although macroscopically normal, was non-functional. The syndrome became known as Arbuthnot Lane's disease. In the absence of a pathognomonic test we will never know whether the disease he treated (with some success) is the same as that which we now call idiopathic slow-transit constipation (ISTC). Equally, in the absence of histology that identifies a pathological abnormality, we do not know whether the condition that we treat 80 years on, with no greater a success rate, is Arbuthnot Lane's disease[5,6].

ISTC is currently defined as a disorder of normal colon propulsion that results in severe constipation. By convention, the condition excludes megarectum and megacolon.

Pathophysiology

Constipation is a common clinical complaint, but what the patient means by the term is often unclear[7]. Normal bowel function is difficult to define, but most people defaecate between three times a day and once every 3 days[8,9]. Marginal infrequency beyond this may be attributed to poor diet and frequently responds to bulk laxatives[10]. Many other constipated patients who do not respond to bulking agents find that symptoms improve with cisapride[11]. Clinicians are increasingly recognizing a group of patients with severe chronic constipation whose symptoms are not helped by bulking agents, prokinetic drugs or other laxative therapy. These patients, who are invariably women, defaecate as infrequently as once every 3–4 weeks and seldom without the aid of an enema or anorectal digitation. On taking a detailed history, two groups of patients may be distinguished. First, there are those whose symptoms date from their adolescence or earlier and whose condition has progressively deteriorated with time[12–14]. In contrast, women in the second group attribute the onset of the condition to a recognizable event, such as pelvic surgery or childbirth. Women in the first group are defined physiologically as having delayed colonic transit[15–17], i.e. ISTC, and those in the second by an inability to expel a balloon from the rectum, implying a rectal–pelvic floor dysynergia[18–21], i.e. outlet obstruction constipation. The picture is confused by the observation that some patients with evidence of ISTC also appear to have features of outlet obstruction constipation[22,23]. Patients with delayed colonic transit with or without outlet obstruction should be classed as having ISTC, while those with outlet obstruction constipation alone should not be included in this nosological category.

Patients who suffer from ISTC often complain of urological symptoms. Urodynamic studies demonstrate detrusor dysfunction, indicating that an abnormality of the autonomic nervous supply to the bladder may be present[24,25]. Further investigations have shown that denervation in the bladder often coexists with rectal denervation[26], consistent with Cannon's law of denervation hypersensitivity[27,28]. In contrast, studies performed in patients who attribute their symptoms to childbirth suggest that there is resulting obstructed urinary flow that cannot be accounted for on the basis of autonomic neuropathy[29]. This might be explained by primary damage to the pelvic floor during a traumatic second stage in childbirth, resulting in dysynergia of rectal and urethral emptying mechanisms.

The pelvic floor and its nerve supply are at risk during prolonged labour and in some cases even normal childbirth is associated with a permanent change in pelvic floor anatomy and physiology[30]. The recent observation[31] that a denervation injury can result following hysterectomy lends some support to the hypothesis that trauma can result in disordered rectal physiology. More recent studies in an animal model have demonstrated that afferent input emanating from one pelvic organ may reflexly inhibit motility in another[32]. The bladder, vagina, uterus and rectum appear to be physiologically linked, and surgery to one structure may alter afferent or efferent function in an adjacent organ. However, patients with constipation after hysterectomy appear to be clinically indistinguishable from those in whom the condition arises *de novo*[33]. In addition, other workers have shown that urological symptoms attributed to hysterectomy are often present before surgery, but are given heightened significance afterwards[34]. The same may be true of constipation.

The source and distribution of both the sympathetic and parasympathetic supply to the left colon and rectum are now more clearly understood. Injury to the autonomic supply to the pelvis and rectosigmoid may occur during pelvic surgery[35,36]. Experimental work has shown that, following such injury, subsequent imbalance of reinnervation with proportionally more sympathetic nerve fibres may contribute to dysfunction[37,38]. It has been shown in patients that resection of the rectosigmoid may interrupt the pelvic nerves in their course through the left colon[39,40], and rectal surgery is often associated with the development of constipation[41].

The aetiology of outlet obstruction constipation is often apparent; patients attribute the onset of symptoms to

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hysterectomy or childbirth. However, it is more difficult to explain logically the aetiology of slow-transit constipation that coexists with pelvic floor dysynergia.

Childhood constipation is not sex specific and yet those presenting with ISTC are almost exclusively female. It is tempting to 'blame it on the hormones', with the onset of menstruation acquiring particular significance. Progesterone in pharmacological doses has been shown[42,43] to relax both animal and human colonic smooth muscle *in vitro*. Similarly, the *in vitro* responsiveness of ileum and colon to acetylcholine is reduced in the presence of progesterone[44]. A similar picture has been demonstrated in the smooth muscle of the gallbladder and at the gastro-oesophageal junction, which implies that progesterone may have an inhibitory effect on the whole gastrointestinal tract[45]. Although some women do suffer from constipation during pregnancy, the precise aetiology is unclear. Abnormally high concentrations of the sex hormones have been detected in the urine of women with severe constipation, but this may be related to abnormal enterohepatic circulation and may not be the primary cause. Sex hormones appear to have little effect on the colonic motility of non-pregnant healthy women, as colonic transit is unaffected by the menstrual cycle[46]. However, a role for the sex hormones in severe constipation has not been established.

Routine light microscopy usually fails to identify a persistent abnormality in the severely constipated colon. The first reported histological abnormality was by Dyer and colleagues[47] in 1969. This comprised thickening of the circular smooth muscle, a reduction in the number of axons and neurones, which were often misshapen, and Schwann cell hyperplasia. In a recent study Krishnamurthy *et al.*[48] noted changes in the myenteric plexus of patients with idiopathic constipation that appeared to be distinct from other pseudo-obstruction syndromes[49-52]. Confirming the previous observation of Dyer *et al.*, they noted a reduction in the total number of argyrophilic neurones, coupled with a morphological abnormality. The total number of axons was also decreased and there was variability in the size and chromatin content of the nuclei. However, they did not report the circular muscle hyperplasia and Schwann cell hyperplasia previously identified by Dyer *et al.*[47]. The findings of Krishnamurthy and co-workers were distinct from previous reports of patients with megacolon, which identified pathology in hypertrophy of the smooth muscle layer[53]. A third study of four adults with organic constipation supported these findings: Smith and colleagues[54] reported a quantitative decrease in the number of argyrophilic neurones but no Schwann cell hyperplasia.

The advent of special stains has now opened the door for the re-exploration of the morphology of the severely constipated colon. The absence of an extrinsic nerve supply in the colon of some patients with long-standing constipation is an exciting discovery[55]. Furthermore, Koch *et al.*[56] showed that the levels of vasoactive intestinal peptide (VIP) and peptide histidine–methionine were reduced in a small series of patients with severe constipation. In addition, they demonstrated that VIP-containing nerves were absent from the circular smooth muscle. This observation has been supported recently in a study by Milner *et al.*[57], who reported reduced levels of VIP in the sigmoid colon of patients with ISTC. As VIP is thought to be a non-adrenergic non-cholinergic inhibitory transmitter intrinsic to the production of the peristaltic wave, its absence could point to the primary pathology in ISTC. Other evidence exists for a functional cholinergic deficit in patients with severe constipation[58].

The extent of the pathology has not been clearly established. The proximal gastrointestinal tract has not been adequately studied in ISTC, but some series have reported oesophageal dysmotility in a proportion of patients[48]. This suggests that, in some patients at least, ISTC may represent the most prominent feature of a pangastrointestinal tract disorder. Considering the multiple aetiologies of this condition, there may be a variety of pathologies and unravelling the neuropathology remains a considerable challenge.

Diagnosis

In screening patients with constipation, radiological marker studies and videoproctography form the basis of investigation. Many patients thought to suffer from ISTC have the diagnosis excluded following normal transit studies. Significant delay in colonic transit can be identified using the technique originally described by Hinton *et al.*[59]. The presence of 80 per cent of radiological markers in the left colon 5 days after ingestion suggests the diagnosis, and their persistence on days 7 and 10 confirms it. A modification of this technique, involving taking three different markers on consecutive days, enables measurement of segmental transit[60]. This modification may be helpful in identifying right- and left-sided colonic delay[61].

Videoproctography is now preferred to balloon proctography by some clinicians for diagnosing outlet obstruction constipation following the observation that normal control subjects sometimes have difficulty expelling a balloon from the rectum. Although failure to open the anorectal angle is of debatable significance, inability to evacuate the rectum of liquid barium is a reliable indicator of pelvic floor dysynergia. Electromyography is used by some clinicians to examine the external anal sphincter and contractility of the puborectalis. Whereas changes in electrical activity have been demonstrated in the sphincter mechanism during simulated defaecation, the same changes have also been reported in normal volunteers. This might be explained by the presence of subclinical disease in some of the controls. Alternatively, it is perhaps expecting too much of asymptomatic people to behave in a physiological manner with needles in the perineum. More importantly, the results of electromyography do not always correlate with those of manometry or videoproctography, or indeed symptoms, and so the value of any of these measurements in isolation is questionable[62].

Colonic motility may be further examined in ISTC by use of colonic manometry. The passage of a nasal catheter into the right colon or a rectal catheter into the left colon has been used for research purposes[63-65]. Such studies suggest that dysmotility may be either total or regional, due to hypersegmentation as opposed to hyposegmentation, or to infrequent or absent mass movements. Potentially useful information from colonic manometry is undermined by the infrequent nature of events and by the fact that segmental colonic contraction may not cause a rise in intraluminal pressure, the pressure being dissipated by adjacent segmental relaxation. Similarly, the abnormally high pressure recordings that are sometimes detected in the sigmoid colon may be due to kinking of water-perfusion catheters as they descend into the pelvis. Likewise, high pressures in a particular region of the bowel may result from recording through a side channel as opposed to an end port, the first being more likely to record wall pressure and the second true intraluminal pressure. Thus, care is needed to determine the significance that should be placed on the magnitude of pressure rise in any particular area of the colon. Perhaps it is more important to note qualitative differences, such as whether pressure waves are present or not and whether they represent prograde or retrograde movement[66].

Whichever way the colon contracts, one of its roles is to transport colonic contents from the caecum to the rectum, and much might be learned from observation of this task. The imprecise and infrequent nature of events makes continuous monitoring difficult. However, in a well designed study of a small number of patients, Kamm *et al.*[67] artificially reduced the period of colonic transit by stimulating the caecum with bisacodyl and observing with a γ camera the subsequent passage of a radionuclide tracer through the colon. They demonstrated that some patients with severe constipation had motility patterns in the right colon and transverse colon that were comparable to those of normal controls, with abnormal patterns confined to the distal colon or rectum. Other patients appeared to have an abnormal motility pattern in the whole colon. The former observation might support the results of other studies[31] that have implicated pelvic denervation as the cause of left-sided constipation. It is interesting to speculate that the latter observation may reflect the situation in pure ISTC.

Treatment

Surgery for severe constipation has been loosely based on a concept of the pathology. Colectomy and ileorectal anastomosis has remained the treatment of choice for ISTC in preference to other surgical options such as limited resection[5]. A satisfactory outcome is achieved in the majority of patients, but a small number are still unable to defaecate after ileorectal anastomosis[5,6,68]. The reason for this is unclear but in some patients there is spasticity of the rectum with pseudo-obstruction of the distal ileal segment. For this reason some authors[69] have recently used proctocolectomy and ileoanal pouch formation for ISTC. Such an approach is not without problems, such as urgency, faecal incontinence and recurrent obstruction, which may eventually result in a permanent ileostomy. The delivery of fluid stool to the rectum may overwhelm the outlet obstruction, as it is intended to do, but, if the sphincter mechanism has been damaged by repeated straining, surgery may succeed only in converting a chronically constipated patient into a faecally incontinent one. It is therefore vital to be able to measure sphincter function before surgery. Where the dysmotility is segmental rather than total, removal of the colon may represent surgical overkill. Recent reports have suggested that left hemicolectomy and excision of the upper rectum can be successfully employed where dysmotility is confined to the distal large bowel[70].

Where outlet obstruction constipation occurs in combination with slow transit, surgery is directed towards the colon and the pelvic floor is ignored. However, where the primary pathology was thought to have its origin in the pelvic floor, surgery has been directed towards the local problem. Previous attempts to deal with outlet obstruction by division of the puborectalis muscle have met with mixed results. The rationale for doing this is to decrease the pressure in the anal canal during defaecation. In practice, incontinence of flatus and mucus have occurred too frequently for the operation to have increased in favour[71–73]. Similarly, the poor long-term results of anorectal myectomy do not justify its 10 per cent incontinence rate, and this operation has been abandoned[74]. Attempts to treat outlet obstruction constipation with locally acting neurotoxin have also been unsuccessful in the long term[75]. The presence of a strong psychological overlay in many patients has prompted some workers to treat this component using biofeedback techniques, with some success[74]. Anismus in these cases is considered to be a learned response, possibly secondary to painful defaecation. Contraction of the external sphincter during defaecation persists, despite the cause being removed. As only the striated muscle is involved, this should be amenable to modulation by biofeedback[76]. Although initially labour intensive, early results are promising and sustained improvement has been reported[77–79]. However, the ability to pass a rectal balloon is not dependent on the coordinated function of the puborectalis and external sphincter alone[78]. Biofeedback may be of benefit in the group of patients who are unable to empty a loaded rectum, but results are poor in ISTC in which the problem is not how to empty the rectum but that the rectum is often empty.

Future prospects

At present, the investigation and management of ISTC is based on a thorough history, videoproctography and transit studies (either total colonic or segmental). However, some patients fail to benefit from surgical treatment and it is important to establish whether they suffer from dysmotility of the more proximal gastrointestinal tract. The authors' clinical impression accords with the findings of others, that some patients with ISTC have proximal disease affecting to a varying extent the oesophagus, stomach and small bowel[48]. These patients might not benefit from colectomy and ileorectal anastomosis, as the proximal dysmotility may form the major component of their disease. Measurement of gastric emptying and small bowel transit will identify such patients, in whom more observation is needed to determine the natural history of the disorder.

Some patients fail to evacuate following ileorectal anastomosis; contrast studies have shown that the rectum fails to admit ileal contents and is spastic in appearance, the adjoining ileum becoming markedly dilated[5]. These patients might be identified by a combination of anorectal manometry and neostigmine–carbachol sensitivity testing. The presence of rectal hypersensitivity might persuade the surgeon to remove the rectum in addition to the colon, leaving the patient with an ileal pouch.

The advent of total colonic manometry might help to elucidate the regional nature of ISTC, if indeed there is one. The technology is now available to measure colonic motility over a 24-h period. Responses to stimuli, both natural and pharmacological, can be measured on a regional basis, and the localization of areas of dysmotility may offer the possibility of a more precise and limited resection. It is perhaps time to evaluate all the various investigations in relation to each other and to establish the best management protocol. We may still find ourselves depending on a clinical history, transit studies and videoproctography, but the exercise is worth pursuing. In addition, neuroendocrine histology must be painstakingly performed on all resected specimens and the results correlated with presentation, investigation and outcome.

To remove the colon in severe constipation is a surgical option but it has little scientific basis. Failure to define clearly the nature and extent of the pathophysiology will result in the condition continuing to be known as Arbuthnot Lane's disease. While this is unimportant for the majority of patients for whom we get it right (like Arbuthnot Lane), it is very important for the smaller number for whom we get it wrong.

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Paper accepted 19 March 1993

Editors' announcement

Case Reports

It is the policy of the Editorial Board of the Journal to limit strictly the number of Case Reports that appear in each issue. During recent months we have been inundated with Case Reports; consequently there has been a very high rejection rate. We remain interested in receiving Case Reports of particular novelty or rarity, but brevity is another criterion of increasing importance. Contributors should note that a succinct Case Report can be used to fill a page that would otherwise be largely empty. To meet this requirement, it has proved necessary to tighten the existing guidelines for Case Reports. From now on they should be no more than 400 words in length or no more than 300 words if a figure is included. The existing limit of five references remains. We strongly encourage contributors to observe these new guidelines so as to avoid automatic rejection of their Case Reports.

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Digests

Der Chirurg

Zeitschrift für alle Gebiete der operativen Medizin
Organ des Berufsverbandes der Deutschen Chirurgen e.V.
Organ der Deutschen Gesellschaft für Chirurgie

Br. J. Surg. 1993, Vol. 80, September, 1112–1114

For this quarter's digest Professor Christian Herfarth and Dr Thomas Lehnert have selected from the April to June issues of Der Chirurg. *The best of the* BJS *for the same period appears in the German journal this month.*

Laparoscopic surgery

Cholecystectomy

The past months' issues of *Der Chirurg* carried a total of 14 contributions in the field of laparoscopic procedures. To determine the current status of surgery for gallstones in Germany a group from Munich[1] sent out questionnaires containing 28 questions to 449 surgeons. A total of 188 complete returns were evaluable and contained information covering 17 232 hospital beds with 405 668 operations performed in 1991. Some 27 403 of these operations (7 per cent) were performed for gallstone disease and 84 per cent represented simple cholecystectomy without exploration of the common bile duct (CBD). In all, 43 per cent of surgeons claimed to have had previous experience with laparoscopic cholecystectomy, 28 per cent started the technique during the observation period and 11 per cent indicated that they would soon start laparoscopic cholecystectomy. It was estimated that in 1993 more than 90 per cent of surgeons will have experience with laparoscopic cholecystectomy. Between 50 and 60 per cent of surgeons would not consider laparoscopic cholecystectomy for patients with cholecystitis, coagulation disorders, choledocholithiasis or previous abdominal operations. Only 6054 of the reported operations (25 per cent) were performed laparoscopically, with a conversion rate to open cholecystectomy of 6·8 per cent. Causes for conversion were adhesions, bleeding and technical problems. Injury to the CBD was recorded in 36 instances. Overall, 98 per cent of surgeons considered preoperative ultrasonography mandatory for the open and laparoscopic procedures. Preoperative intravenous cholangiography was considered necessary by only 11 per cent of surgeons for open cholecystectomy whereas 51 per cent considered this procedure necessary before laparoscopic cholecystectomy. In patients with isolated CBD stones (e.g. after cholecystectomy) most surgeons (61 per cent) favoured endoscopic retrograde cholangiography (ERC) plus endoscopic papillotomy. Intraoperative cholangiography was routinely performed by 80 per cent of surgeons during open surgery, but by only 2 per cent during the laparoscopic operation. If patients present with a combination of cholecystolithiasis and CBD stones most surgeons (44 per cent) performed open cholecystectomy and exploration of the bile ducts. Only 7 per cent would remove the gallbladder laparoscopically and resort to postoperative ERC plus papillotomy. Rates of postoperative complications were similar for open (8·7 per cent) and laparoscopic (6·8 per cent) cholecystectomy, although slightly more patients required relaparotomy after the laparoscopic procedure (1·5 *versus* 0·8 per cent). The mortality rate was 0·14 per cent after laparoscopic and 0·43 per cent after open cholecystectomy.

A similar retrospective survey[2] was performed in Austria in 1991. The questionnaire contained only 17 questions and was honoured by a 100 per cent return rate. Of 13 763 cholecystectomies performed in 1991, 7351 (53 per cent) were undertaken laparoscopically. The conversion rate to open operation was 2·1 per cent mostly because of bleeding or injury to the CBD. Findings from the Austrian study were similar to those of the German survey in that 99 per cent of surgeons required preoperative ultrasonography. Again, 80 per cent of patients scheduled for laparoscopic cholecystectomy underwent intravenous cholangiography. Relaparotomy after laparoscopy was required in 66 patients (0·9 per cent) and the mortality rate after laparoscopic cholecystectomy was 0·05 per cent (four patients). The mean hospital stay was 4·5 days and only a few procedures were carried out on an outpatient basis.

A large survey from Switzerland[3] recorded data prospectively from members of the Swiss Working Group on Laparoscopic and Thoracoscopic Surgery. A total of 3722 laparoscopic cholecystectomies were performed in the 50 member institutions between November 1989 and February 1992. Some 1268 open cholecystectomies were carried out during the same period in these departments. All patients had preoperative ultrasonography and 82 per cent were examined by intravenous cholangiography. The conversion rate to open cholecystectomy was similar to that of the German retrospective experience at 7 per cent. Postoperative complications were noted in 87 patients (2·3 per cent) and 39 (1·0 per cent) required relaparotomy within 30 days, the most frequent indication being injury to the bile ducts or leakage. Three patients died after operation, giving a mortality rate of 0·08 per cent.

A group from Munich[4] provide a comprehensive review of the literature on open and laparoscopic cholecystectomy published between 1986 and 1992, and conducted a postal survey by sending a questionnaire to 22 German centres experienced with the laparoscopic procedure, collecting data on approximately 13 000 patients treated between 1990 and 1992. For open cholecystectomy ($n = 18017$) the authors calculated a complication rate of 5·8 per cent and mortality rate of 0·5 per cent. The respective figures for laparoscopic cholecystectomy ($n = 25644$) were 4·4 and 0·09 per cent. In the collected series from 22 centres with a special interest in the laparoscopic method the complication rate was 5·3 per cent and the mortality rate 0·1 per cent. The authors stress that proper patient selection and care to avoid bile duct injury are mandatory to maintain good results from laparoscopic techniques. Injury to the CBD was often recognized late and they suggest that any deviation from a smooth postoperative course should prompt immediate investigation.

Herniorrhaphy

Laparoscopy has also been applied for inguinal hernia repair. Papers from Austria, Switzerland, France and Germany[5–8] describe prosthetic mesh reinforcement of the inguinal region. A group from Vienna[5] give technical details of the open technique of preperitoneal mesh reinforcement. A large mesh is used to reinforce the symptomatic and contralateral sides, even if there is no clinical evidence of herniation at the latter. Polyester mesh is preferred over polypropylene since its texture allows it to remain in place without additional suturing. Although predominantly employed for recurrent hernia the technique was used for primary hernia with good short-term results.

A paper from Aarau, Switzerland, reports results of a prospective study of open mesh repair for recurrent inguinal hernia[6]. Using a similar preperitoneal approach in 47 patients with recurrent hernia the authors recorded no postoperative infection. One patient required drainage of wound seroma. All patients were followed for a median of 20 (range 12–60)

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months. Only one patient had another recurrence at 6 months, which was successfully repaired using an anterior approach.

The same preperitoneal mesh repair was performed laparoscopically by a French group[7] in 93 patients with 110 inguinal hernias. These authors used a polypropylene mesh, which was stapled in place using a three-cannula technique. With growing experience the average time for the procedure now is 30 min.

Experience with laparoscopic preperitoneal mesh repair in 59 German patients was also reported[8]. There was a 25 per cent recurrence rate when an absorbable mesh prosthesis was used in the first 16 patients. Using a polypropylene mesh with extensive fixation (ten to 14 staples), no further recurrences have occurred to date in 57 operations. No deep infection of the prosthetic material was recorded although one patient had infection of the trocar site.

Opponents of mesh repair techniques consider infection of the graft material and hernia recurrence the two major potential problems. Although long-term recurrence rates for the new methods cannot yet be documented, the low perioperative infection rates are encouraging; late infection may, however, become apparent only after several years.

Fundoplication

DeMeester and Peters[9] reviewed the current indications for gastro-oesophageal antireflux procedures and noted that good results depend on proper patient selection. Patients with normal peristalsis of the lower oesophagus were treated by a 360° Nissen fundoplication performed laparoscopically. For those with compromised peristalsis or aperistalsis the authors recommend an open Belsey procedure using a transthoracic approach. Patients with brachyoesophagus are not deemed candidates for the laparoscopic operation and in those with acid hypersecretion addition of a vagotomy is suggested. The review of criteria for patient selection is followed by a well illustrated step-by-step description of laparoscopic Nissen fundoplication.

Deep vein thrombosis

Low-dose heparin prophylaxis is standard treatment for hospital patients in the postoperative period. In ambulatory medicine no clear treatment policy has been established for patients requiring prolonged immobilization of fractured extremities but who do not require hospitalization. A group from Essen[10] in 1991 embarked on a randomized controlled trial to answer two questions: (1) What is the incidence of deep vein thrombosis (DVT) in ambulatory patients with immobilization of the lower extremity for 'minor' injury?; and (2) Can low molecular weight heparin (LMWH) prophylaxis reduce the incidence of thrombosis in these patients? Prospective candidates for the trial were studied by duplex ultrasonography and a number of other tests to exclude pre-existing DVT before randomization to heparin or no treatment. Treatment consisted of a daily subcutaneous dose (0·3 ml) of LMWH equivalent to 1500 aPTT units and 3000 anti-Xa units. Most patients were instructed in self-injection. The first dose of heparin was administered on the day the cast was applied and the last given on the day it was removed. Sex distribution, average age, height and Broca index were comparable for the two groups. Potential risk factors for the development of DVT such as smoking, obesity, presence of varicose veins and contraceptive use were comparable in both groups. During the study period 306 patients were considered eligible for the trial. Twenty-seven patients were excluded, because of risk factors precluding heparin treatment. Thirty-eight randomized patients were not evaluable, because they were operated on at a later stage ($n = 14$), did not attend the final examination ($n = 21$) or switched treatment groups ($n = 3$). A total of 241 evaluable patients thus completed the study (treatment group, 115; control group, 126). The total time of immobilization was 15 days in patients given heparin compared with 18 days in those not so treated. No patient in the treatment group was found to have developed DVT compared with five of 126 (4·0 per cent) controls ($P = 0{\cdot}04$). No correlation could be established between the duration of immobilization and the incidence of DVT, with three of five instances of thrombosis diagnosed in the first week of immobilization. No severe side-effects of heparin treatment were recorded. The authors conclude that one daily self-application of LMWH is safe and effective in preventing DVT in outpatients requiring plaster immobilization of the lower extremity.

Soft tissue sarcoma

The June issue carries the first part of a series of leading articles on soft tissue sarcoma. Murray Brennan[11] reviews the vast experience of the Memorial Hospital, New York, with soft tissue sarcoma in 2044 patients treated between 1982 and 1992. Multivariate analysis determined tumour grade, deep location and size >5 cm as independent prognostic factors of survival and development of metastases. Management strategies focus on multimodal therapy. An ongoing prospective randomized study of adjuvant brachytherapy has demonstrated reduction of local recurrence rate in high-grade tumours, although long-term survival was not significantly improved. It also emerged from the data that small ($\leqslant 5$ cm diameter) soft tissue sarcoma of the extremities has a favourable 5-year survival rate of 94 per cent irrespective of tumour grade, depth, location or type of surgical treatment and should, therefore, not be included in future randomized trials studying adjuvant treatment.

A paper from the University of California at Los Angeles[12] reports preliminary results of a prospective study of adjuvant preoperative and postoperative radiochemotherapy for high-grade soft tissue sarcoma. Between 1989 and 1992, 42 patients with tumours of various location and histological origin were recruited. Radiochemotherapy consisted of two 6-day courses of ifosfamide (14 g/m^2) and a third 2-day course of cisplatin (120 mg/m^2) plus doxorubicin (60 mg/m^2). In addition, patients received radiotherapy with 40–50 Gy (T-18 protocol). After surgical removal of the tumour the course of chemotherapy was repeated. All patients completed the preoperative treatment course and 31 of 42 completed the postoperative chemotherapy. At a median follow-up of 2 years no patient had developed local recurrence. Three patients died during follow-up, giving an overall survival rate of 93 per cent, while the recurrence-free survival rate was 86 per cent.

It would seem that progress is being made and the second part of this series on soft tissue sarcoma to be published in the July issue of *Der Chirurg* is anticipated.

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The American Journal of Surgery

The April to June issues of The American Journal of Surgery *form the basis for this quarter's digest prepared by that journal's Editor, Dr Hiram C. Polk Jr. A summary of the same months'* BJS *by our own Professor John Farndon appears in the September issue of the American journal.*

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Laparoscopic cholecystectomy

The April issue[1] consists of papers presented at the Consensus Conference arranged by the National Institutes of Health in Bethesda, Maryland, on 14–16 September 1992, attempting to put laparoscopic cholecystectomy into perspective. It addresses issues of the pathogenesis of gallstones, the non-operative care of patients and the combined use of laparoscopic and endoscopic techniques, and draws a reasonably careful set of conclusions regarding the role of these less invasive procedures for biliary tract disease in 1993. The NIH Consensus Conferences have evolved over the past decade as an important mechanism for bringing mainstream medical and scientific thought to the public's attention. The even-handedness and breadth of material in the special issue is impressive.

Pancreatic cancer

The role of the Whipple operation has been a subject of surgical thought for many years. The critical issue in managing cancer of the head of the pancreas is in establishing its resectability and lack of involvement of vital structures such as the superior mesenteric vein. Papers from the Virginia Mason Clinic, under the leadership of Traverso, have often focused on such issues. A report from the North Pacific Surgical Association describes the relative value of contrast-enhanced computed tomography (CT) *versus* angiography and clinical observation at surgery[2]. CT detected vascular invasion that had been overlooked on angiography in 20 per cent of patients and angiography detected invasion indicating inoperability in 5 per cent. There were other CT criteria of irresectability in this 5 per cent of patients and angiography provided no supplemental staging information. The authors conclude that CT accurately predicted irresectability in every patient and that resectable tumours were identified in 72 per cent of cases.

The same group examined visceral angiography as an aid to intraoperative surgical decision making in a similar group of patients[3] and concluded that 30 per cent of 64 angiograms showed a significant vascular abnormality requiring specific preoperative or intraoperative measures. This particular group recommends the advantages of contrast-enhanced CT as an initial screen for resectability and suggests that angiography is helpful in selected patients to guide the operative strategy.

Portal hypertension

The imagination of the interventional radiologist has led to the transjugular intrahepatic portacaval shunt to provide portal decompression without operation. The University of Washington faculty at Seattle describe experience in which 93 per cent of 59 consecutive patients ultimately received successful shunting although one-third required more than one procedure[4]. The 25 per cent hospital mortality rate was not related to Child's grade but to the presence of haemorrhage at the time of the attempted shunt procedure. Some 12 per cent of patients developed early occlusion of the intrahepatic shunt. The place of the procedure alongside sclerotherapy and conventional surgery, which preserve hepatopedal blood flow, remains to be defined.

Dialysis

Erythropoietin has been a broadly used agent to treat the anaemia intrinsic to chronic renal failure. Examining shunts used for chronic haemodialysis, the Portland group showed that suspicions of an increased rate of thrombosis of dialysis grafts are unfounded[5]. This verifies the absence of a serious side-effect of erythropoietin but does not address its cost-effectiveness.

Complications of biliary procedures

The relative role of endoscopic retrograde cholangiopancreatography (ERCP) with laparoscopic cholecystectomy in the treatment of operative complications is not defined. There is a

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growing incidence of acalculous cholecystitis in patients treated laparoscopically, a number that may have increased more than fivefold compared with that of the open operation. The group at the Virginia Mason Clinic in Seattle describe experience with ERCP after laparoscopic cholecystectomy[6]. This was an effective technique for dealing with several injuries, including those to the bile duct that required stenting and papillotomy. They concluded that surgery could be avoided in a large number of patients.

Ress *et al.*[7] from the Mayo Clinic provide their first report on the early management of major injuries occurring during laparoscopic cholecystectomy. Approximately half the patients were treated by definitive bile duct reconstruction. The emphasis on long-term and definitive repair was clear.

Soper *et al.*[8] at Washington University describe a similar number of patients with biliary complications incidental to laparoscopic cholecystectomy. The majority of patients were treated by combined radiological, endoscopic and operative therapy. They identified the most common error in the initial operation to be mistaking the common bile duct for the cystic duct, and stressed the importance of a multidisciplinary approach to the patient who is suspected of having sustained such an injury.

The combination of the laparoscopic surgeon with someone skilled in ERCP has brought skills to bear on a group of patients who were traditionally at very high risk for conventional surgery. There is a small incidence of duodenal perforation associated with ampullary papillotomy. Chung *et al.*[9] at the Cleveland Clinic describe a clinical scenario and suggest that prompt improvement in symptoms within the first 24 h is associated with spontaneous recovery. Operation was recommended when: (1) pain or abdominal signs were prominent; (2) there were signs of intraperitoneal infection; or (3) there was failure to respond to a short trial of non-operative care.

Wound healing

The variety of nomenclature and actions of wound healing factors is complex and challenging. Bennett and Schultz[10] from the University of Florida provide a two-part summary of wound healing as modified by epidermal growth factor, transforming growth factor β, platelet-derived growth factor, insulin-like growth factor and fibroblast growth factor families. This paper is a resource document for those trying to understand wound care and the potential clinical application of these substances. The randomized prospective clinical trial may clarify such issues, although whether one can study wound healing in a 'blinded' study of topical agents remains to be seen. Contemporary reports are filled with small series and/or inadequate controls that trumpet the value of many new treatment protocols. This paper defines in an effective way the range and current potential role of these materials.

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Digest

SURGERY TODAY
The Japanese Journal of Surgery

Br. J. Surg. 1993, Vol. 80,
September, 1116–1117

Professor Yoshio Mishima has this month selected from the April, May and June issues for his digest from Surgery Today (The Japanese Journal of Surgery).

Oncology

Oka *et al.*[1] investigated the immune function of peripheral blood cells and cells from the pleural and abdominal effusions of patients with advanced cancer. This was compared with function of peripheral blood cells from controls. The parameters examined included lymphocyte subsets, natural killer (NK) cell activity, and anti-DAUDI and lymphokine-activated killer (LAK) cell activity. The percentage of CD4$^+$ pleural and peritoneal exudate cells was significantly higher than that of peripheral blood mononuclear cells (PBMCs) in patients. The proportion of CD8$^+$CD11$^+$ pleural and peritoneal exudate cells and PBMCs (suppressor T cells) of patients was increased compared with controls. The percentage of CD8$^+$CD11$^-$ pleural and peritoneal exudate cells (cytotoxic T cells) was identical to that of the PBMCs of patients and controls. The NK cell activity of pleural and peritoneal exudate cells was significantly lower than that of PBMCs in both patients and controls, and there was no correlation between the NK cell activity of PBMCs and pleural and peritoneal exudate cells. Although the anti-DAUDI activity of pleural and peritoneal exudate cells was markedly low, LAK cells with high activity could be induced by culture with interleukin (IL) 2 for 4 days. These results suggest that the immune function of cells in malignant effusions may be depressed because of a low population of cytotoxic T cells, low NK cell activity and increased suppressor T cells, while the local administration of IL-2 may induce LAK cells. Effective local immunotherapy for malignant effusions should augment effector cells and inhibit suppressor cells.

COL-2-JCK, a human colonic cancer xenograft line that can be transplanted into nude mice, was implanted in the subserosal layer of the caecum, either as tumour tissue or as a single cell suspension. When cancer tissue was used for the caecal implantation, 100 per cent extensive local tumour growth and a high incidence of metastasis to the regional lymph nodes, peritoneum, liver and lung were observed. In contrast, when the COL-2-JCK cell suspension was injected into the caecal wall, no metastases were observed, with significantly reduced local tumour growth. Experimental studies should maintain the original tumour tissue structure to allow full expression of the biological characteristics of the cancer phenotype. According to Furukawa *et al.*[2] this nude mouse model of caecal implantation might allow better understanding of the biology of human colonic cancer.

Transplantation

Ohzato *et al.*[3] evaluated sequential serum IL-6 levels in the diagnosis of hepatic allograft rejection. This study was conducted in nine cynomologous monkeys that had undergone orthotopic hepatic allotransplantation, six of which were treated with FK-506 (a new immunosuppressant agent isolated from *Streptomyces tsukubaensis*) and three of which were not. The untreated animals showed biochemical abnormalities from days 5 to 6, characterized by a marked increase in serum alkaline phosphatase levels. These animals died on days 8, 12 and 63 (group I). Acute cellular rejection was confirmed by histological study of the hepatic grafts taken at autopsy or biopsy. Four of the treated animals (group IIa) survived more than 30 days and had a slight increase in alkaline phosphatase level (<2000 units/l). Histological examination at 30 days after transplantation revealed a transient infiltration of polynuclear cells into Glisson's area, with the portal vein and bile duct remaining intact. The remaining two animals (group IIb) died from dehydration and arterial thrombosis on days 5 and 7. A kinetic study of serum IL-6 conducted during the first 2 weeks showed quite different patterns among the three groups. All recipients in group I demonstrated two peaks following grafting, on days 1 and 3 or 4, the second peak of above 2·0 units/ml preceding biochemical abnormalities by 2–3 days. Conversely, the recipients in group IIa showed a single peak of serum IL-6 on day 1, followed by a decrease to less than 2·0 units/ml. Group IIb characteristically showed a high level of serum IL-6 on day 1, after which the value remained above 2·0 units/ml. The monitoring of serum IL-6 proved useful for detecting the acute rejection of hepatic allografts, the recipients with rejected grafts displaying two peaks of the interleukin. The first rise was observed on day 1, which might reflect the stress of the surgical procedure. The second transient increment was seen on day 3 or 4 and might suggest acute hepatic rejection, preceding biochemical abnormalities by 2–3 days.

Gastric cancer

The long-term effects of gastrectomy on nutritional and immunological status were investigated by Tsuburaya *et al.*[4]. The study was prospective in 79 patients with gastric cancer who underwent curative gastrectomy and were followed after operation for an average of 5 years 3 months. The proportion of actual body-weight to normal weight before illness was less than 95 per cent in 80 per cent of the study patients. Levels of retinol-binding protein, prealbumin and albumin were lower than normal in 17, 26 and 26 per cent of patients respectively. The mean values of the percentage of normal weight, and levels of retinol-binding protein and prealbumin were significantly lower in those undergoing total than in those undergoing subtotal gastrectomy (P < 0·01). The method of reconstruction did not affect the nutritional status except for the prealbumin level, which was significantly lower in patients with Roux-en-Y procedures than in those with interposed segments after total gastrectomy. Cell-mediated immunological alterations after gastrectomy were observed in 31, 37 and 71 per cent of all patients for the OKT3 subpopulation, OKT4:OKT8 ratio and blastogenesis by phytohaemagglutinin respectively. Multivariate analysis revealed that the long-term immunity of patients after gastrectomy was not affected by the levels of albumin and rapid-turnover proteins but by splenectomy and weight loss.

Intestine

To determine the absolute minimum tissue blood flow for safe colonic anastomosis, the wound healing of anastomotic sites with varying degrees of blood flow (measured by laser Doppler fluxmetry) was examined in dogs by Kashiwagi[5]. The correlation between the flux value and tissue blood flow measured by the hydrogen gas clearance method was good (r = 0·91). After transection and anastomosis of the colon with varying degrees of devascularization, anastomotic wound healing was examined. The laser flux values at the anastomotic sites of all dogs in which dehiscence had occurred were less

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than 0·8. In the groups receiving 2 and 4 cm of devascularization, the mean(s.d.) flux values were 1·23(0·34) and 0·88(0·20) respectively. There were significant differences between the latter two groups concerning postoperative course, histological features and hydroxyproline concentration. If the laser Doppler flux value at the anastomotic site is at least 1·0, corresponding to about 30 per cent of the tissue blood flow of the intact colonic wall, the anastomosis is considered to be safe and without risk of dehiscence.

Biliary tract

Bile duct neoplasms occur relatively often in Taiwan in patients with hepatolithiasis. Ker *et al.*[6] studied 49 patients with positive immunoperoxidase staining for carcinoembryonic antigen (CEA) in the bile duct glands in relation to the concentration of CEA in serum and bile. The mean(s.d.) bile concentrations of CEA in 15 control patients, 16 patients with hepatolithiasis, seven with hepatolithiasis and bile duct carcinoma, and 11 with bile duct carcinoma only were 4·09(4·12), 70·49(81·62), 137·73(66·15) and 144·3(117·31) ng/ml respectively. A positive CEA stain from the bile duct was seen in 13, 81, 86 and 91 per cent of each group respectively. No strongly positive stain (grade 2 or 3) was found in the control group but was seen frequently in patients with hepatolithiasis and bile duct carcinoma. This study suggests that there is likely to be an associated neoplasm in patients with hepatolithiasis if the CEA level in the serum or bile is raised.

Breast

Fukutomi *et al.*[7] investigated the relationships between residual cancer and age, tumour location, tumour diameter, mammographic findings, presence of nipple discharge, histopathological type, lymphatic and/or vascular invasion by tumour cells, histological grade, histological lymph node metastases, and oestrogen receptor (ER) status in 1494 patients with breast cancer that involved diagnostic excisional biopsy. Residual cancers were found in 581 of 1448 mastectomy specimens (40 per cent), after 46 (3 per cent) with multicentricity had been excluded. No correlation was observed between residual cancer and age, histological grade or ER status. However, residual cancer rates were significantly higher in patients with tumour diameters $\geqslant$3·1 cm, tumours beneath or in the vicinity of the nipple–areola, malignant calcifications noted on mammography, serous or bloody nipple discharge (particularly with positive cytological findings), papillotubular carcinoma diagnosed by biopsy, lymphatic invasion by tumour cells or a high number (four or more) of lymph node metastases. These seven clinicopathological factors are thus considered useful prognostic indicators for local recurrence in breast conservation therapy with lumpectomy.

Cardiovascular surgery

Aoyagi *et al.*[8] studied 11 patients undergoing replacement of the aortic arch or adjacent areas for aneurysmal disease between 1989 and 1991, using hypothermic cardiopulmonary bypass at 20–23°C with partial brachiocephalic perfusion. Selective perfusion of the innominate artery was performed in all 11 patients through the right axillary artery, while partial brachiocephalic perfusion was carried out using a separate arterial roller pump with a flow rate of 10 ml per kg per min. Direct cannulation to the left common carotid and left subclavian arteries was not performed. There were four men and seven women who ranged in age from 26 to 78 (mean 56) years. The aetiology of aneurysmal disease was aortic dissection in ten patients and aortitis in one. The mean(s.d.) cardiopulmonary bypass time was 214·3(39·3) min, aortic cross-clamping time 131·5(33·4) min and partial brachiocephalic perfusion time 57·6(15·1) min. There were three operative deaths, from multiple organ failure, acute peritonitis and infection of the composite graft in the ascending aorta in one patient each. There were no deaths related to the technique of partial brachiocephalic perfusion and no neurological complications. Partial brachiocephalic perfusion under hypothermic cardiopulmonary bypass is proposed as a safe and effective technique in surgery for aneurysm involving the aortic arch.

Paediatric surgery

It is well documented that piriform sinus fistulas often cause suppurative thyroiditis. The diagnosis is difficult when suppurative thyroiditis does not occur. Hashizume *et al.*[9] describe 11 patients with piriform sinus fistula. A conventional surgical approach was performed in the first eight patients and there were four recurrences in two. A new technique was introduced for the next three patients and for one with recurrence. The internal orifice of the fistula was viewed with a laryngoscope, after which a transverse incision on the neck was made and the abscess dissected. The side wall of the piriform sinus was then opened with the help of a laryngoscope, and the bottom part of the mucosa of the sinus transected with the internal orifice of the fistula. The fistula was then removed *en bloc* with the bottom part of the sinus and abscess cavity. Using this technique no complications occurred and there have been no recurrences so far.

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Acute limb deterioration during intra-arterial thrombolysis

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Approximately 12 per cent of limbs undergoing intra-arterial thrombolysis (IAT) develop distal embolism or extension of thrombus during the procedure. These are usually of little clinical consequence and can be treated by increasing the rate of administration of the lytic agent. However, in some patients the clinical condition of the limb deteriorates rapidly. In an attempt to define the incidence of acute limb deterioration during IAT, information was collected from five centres in the UK with experience of the technique. A total of 866 treatments were recorded, with 20 limbs (2·3 per cent) undergoing acute deterioration. This complication was more common during the treatment of thrombosed popliteal aneurysm than during that of emboli or thrombosed atheromatous arteries or grafts ($P < 0.001$)*. The amputation rate associated with the complication was high, and operative intervention provided better results than continuation of lysis.*

Few surgeons in the UK have a large experience of intra-arterial thrombolysis (IAT)[1,2]. The technique does, however, provide a valuable means of clearing blocked grafts[3], native arteries occluded by embolus or thrombus[4] and thrombosed popliteal aneurysms[5]. Factors influencing success include duration[2] and length[4] of the occlusion, and the state of the run-off[6]. The main complications of the procedure are stroke, occurring in approximately 1 per cent of cases, and major haemorrhage, occurring in 5 per cent. Minor haemorrhage and catheter-related problems have been described in approximately 15 per cent of treatments[7].

Recently, a further major complication of IAT has been highlighted: acute catastrophic deterioration of the limb during treatment. This often occurs at a time when lysis appears to be progressing satisfactorily[8]. This paper describes the combined experience of this type of problem from five centres in the UK; an attempt has been made to define patients at particular risk.

Patients and methods

During September 1992 information was collected from the five participating centres (Reading, Bristol, Nottingham, Guildford, London), all of which had a wide experience of IAT. The number of episodes of thrombolysis, the type of occlusion treated and the number of cases of acute limb deterioration were noted. Some degree of limb deterioration often takes place during lysis. For this study, only limbs that suddenly became non-viable during lysis were included, and a record was made of the treatment and outcome of the complication. Each of the centres recorded data prospectively; details of the techniques used in the different centres are well documented[2,6,9–11].

Results

Table 1 shows the total number of patients in the combined series and the number having acute limb deterioration during lysis. No significant difference emerged between the results of the five centres. The incidence of deterioration due to ischaemia was higher in patients undergoing thrombolysis for thrombosed popliteal aneurysm than in those having treatment of thrombosed atheromatous arteries or grafts ($\chi^2 = 24{\cdot}8$, 1 d.f., $P < 0{\cdot}001$). The median time of onset of acute deterioration from the start of lysis was 9 (range 4–48) h.

Of the 20 patients whose limb deteriorated during treatment, 18 initially presented with rest pain, one with rest pain and gangrene, and one with incapacitating claudication. All but two patients presented within 1 month of the onset of symptoms, 11 within 1 week and six within 24 h. The lytic agent was streptokinase in nine cases, recombinant tissue-type plasminogen activator (rtPA) in ten and acetylated plasminogen–streptokinase activator complex in one. No particular type of catheter was noted to be associated with development of the complication.

Table 2 shows the management and outcome in 19 cases. A further patient who had complete clearance of run-off after thrombosis of a popliteal aneurysm is excluded. This patient's limb deteriorated suddenly towards the end of infusion, despite the angiographic appearance remaining satisfactory. The man developed renal failure as a result of rhabdomyolysis from a compartment syndrome, ultimately dying after fasciotomy and subsequent amputation.

Continuation of lysis with a higher dose of agent resulted in the salvage of two limbs; five were lost and two of these

Table 1 *Incidence of acute deterioration of limbs due to ischaemia during intra-arterial thrombolysis*

	No. treated	No. with acute deterioration
Native artery	710	11 (1·5)
Graft	110	3 (2·7)
Popliteal aneurysm	46	6 (13)
Total	866	20 (2·3)

Values in parentheses are percentages

Table 2 *Management and outcome after acute limb deterioration due to ischaemia in 19 patients*

Outcome	Continued lysis ($n = 7$)	Operative intervention* ($n = 12$)
Limb salvaged	2	6
Amputation	5	6
Death	2†	0

*Includes one percutaneous transluminal balloon angioplasty. †The two who died were among the five who underwent amputation

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patients died. Operation resulted in the salvage of six of 12 limbs with no deaths. No angiograms were taken after deterioration of the limb in the 12 operated patients. However, in the seven patients who were treated by continued lysis, the angiographic findings after the complication occurred included complete occlusion of the calf vessels (two patients), and fresh embolus into the tibioperoneal trunk (four) and calf vessels (one).

Discussion

In this series 2·3 per cent of 866 patients experienced sudden catastrophic deterioration of the limb during IAT. Those with a thrombosed popliteal aneurysm seem to be at particular risk; 13 per cent developed the complication.

Acute limb deterioration during IAT needs to be differentiated from rethrombosis after successful lysis. The latter is not uncommon and has been described in 96 of 386 successfully cleared lesions in one series[4]; it occurs particularly during the first few weeks after completion of lysis. Occlusive problems occurring during IAT are also well described and include pericatheter thrombosis, progression of thrombus and the production of emboli. The review of published papers in *Table 3* suggests that distal embolism occurs four times more commonly than thrombosis. However, pericatheter thrombosis has been described in up to 26 per cent of cases by some[25].

Hess *et al.*[4] subdivided emboli into two types. Microemboli produced transient ischaemia in 46 (7·2 per cent) of 637 treatments. Macroembolism occurred in 43 (6·8 per cent) but was associated with deterioration of the limb in only one case. Embolism or thrombosis occurring during IAT generally requires no treatment other than increasing the rate of infusion of the lytic agent and perhaps positioning the catheter more distally. Fragmentation of the clot to produce emboli is a complication of the lytic process that has been described with both IAT and intravenous thrombolysis[26]. On the other hand, thrombosis may be a risk that is specific to the presence of the perfusing catheter within an artery. Infusing heparin with the lytic agent in an attempt to prevent pericatheter thrombosis has sometimes proved successful[27], but concern has been expressed that a combination of the two drugs may lead to an increased incidence of haemorrhagic complications.

Approximately 12 per cent of patients experience embolism or extension of thrombosis during lysis, but it is apparent that this is associated with no or only transient clinical deterioration in most cases. The present data suggest that about 2 per cent of patients will experience acute limb deterioration, although this will vary depending on case mix. Increasing the rate of lysis is satisfactory for treating asymptomatic or minimally symptomatic occlusions, but appears less satisfactory in the presence of marked symptoms. It was found that rates of both limb salvage and survival were higher in patients treated surgically than in those receiving continued lysis.

Massive distal embolism from thrombus destabilization is probably the commonest cause of this problem, although there may be others. Compartment syndrome after successful IAT requiring fasciotomy is also well documented[17] and acute deterioration may represent a reperfusion syndrome. A further potential problem is blockage of important collateral vessels by the perfusing catheter.

Table 3 *Review of published papers describing 1306 treatments using intra-arterial thrombolysis*[4,12–24]

Complication	No. of patients ($n = 1306$)
Distal embolism	134 (10·3)
Thrombosis	32 (2·5)
Total	166 (12·7)

Values in parentheses are percentages

In conclusion, acute catastrophic limb deterioration occurring during apparently successful thrombolysis is a very real problem of which vascular surgeons and radiologists need to be aware. Despite the higher incidence of the complication in patients undergoing lysis for thrombosed popliteal aneurysm, we still feel that IAT has a role in this condition. The aim of IAT is to clear run-off before ligating the aneurysm and we recommend that, rather than placing the infusing catheter in the superficial femoral artery above the aneurysm, it should (if possible) be passed through the latter so that the calf vessels can be infused directly. An alternative is to infuse either streptokinase or tPA into the calf vessels during the operation after ligating the aneurysm. Early results using this technique are encouraging[28].

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Announcement

The Vascular Surgical Society of Great Britain and Ireland

The Annual General Meeting of the VSS this year will be held at the Royal Northern College of Music in Manchester on 18 and 19 November. Following receipt of a generous offer of sponsorship by The British Journal of Surgery Society, Council has decided that two separate prizes will be awarded for papers presented at the AGM.

The British Journal of Surgery Prize will be awarded for the best paper presented by a surgeon in training on basic or laboratory-based vascular research. The Founder's Prize will be awarded for the best paper presented by a surgeon in training on clinical research. The value of each prize is £500.

Further information about eligibility and instructions for entering will be circulated with the abstract and registration documents for the meeting.

P. L. Harris
Secretary
Vascular Surgical Society
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Sources of air embolization during carotid surgery: the role of transcranial Doppler ultrasonography

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Transcranial Doppler ultrasonography (TCD) has shown that air embolization is relatively common during carotid surgery[1,2] and this may be associated with neurological complications[3]. This report describes three unusual but preventable sources of presumed air embolization, one of which may have caused a minor neurological deficit.

Case reports

Patient 1

A 58-year-old man presented with transient ischaemic attacks (TIAs) in the carotid territory caused by 80 per cent carotid artery stenosis and subclavian steal from subclavian artery origin occlusion. He underwent combined left carotid endarterectomy and left carotid–subclavian bypass. The two carotid procedures were completed first, and carotid flow was restored without ultrasonographic evidence of embolization. However, after subsequent restoration of flow to the arm, TCD detected numerous embolic signals in the ipsilateral middle cerebral artery, suggesting that air had reached this artery via the ipsilateral vertebral artery. The patient suffered no neurological sequelae.

Patient 2

A 62-year-old woman underwent left carotid endarterectomy with a Pruitt–Inahara shunt, having presented with TIAs. At 10 min after shunt insertion, TCD detected numerous embolic signals. No obvious source was identified until it became apparent that they were coincidental with the cardiac cycle (*Figure 1*). Closer examination of the operative field revealed that blood was gradually displacing a column of air in the T limb of the shunt. Following removal of all air from the T limb, no further embolic signals were detected. The patient suffered no neurological sequelae.

Patient 3

A 70-year-old man underwent left carotid endarterectomy with a Pruitt–Inahara shunt, having presented with a stroke and residual neurological deficit. As the vein-patch angioplasty was being anastomosed, the distal shunt balloon deflated and was subsequently refilled on two occasions with heparinized saline. Immediately after each inflation, TCD detected numerous embolic signals in the middle cerebral artery and the shunt was removed. This procedure revealed a distal ballon leak (possibly due to a needle stick); a new shunt was inserted and no further embolic signals were detected. After operation the man had a slight worsening of the pre-existing neurological deficit, but this resolved completely within 72 h.

Discussion

Air or microparticulate emboli cause high-energy signals to be superimposed on the middle cerebral artery waveform together with a characteristic high-pitched sound[1,3]. In patient 1, the subclavian artery had obviously not been completely cleared of air before the restoration of flow, and air entered the middle cerebral artery via the vertebral artery. It is recommended that the T limb of the Pruitt–Inahara shunt is cleared of air before use. We can only presume that the shunt was located at a particular angle during the operation that enabled air in the T limb to be progressively displaced by blood. Although a haemodynamic cause for the neurological deficit in patient 3 cannot be excluded, only a few minutes had elapsed before a second shunt was inserted and insertion was not associated with any TCD embolic phenomena. Moreover, because the embolic signals immediately followed balloon insufflation, it can only be assumed that air was inadvertently included in the balloon-inflating syringe and then expelled through the hole.

In each case, embolization could have been avoided. This experience highlights the benefits of TCD in improving operative technique, particularly as one patient may have suffered neurological complication, albeit minor, as a consequence.

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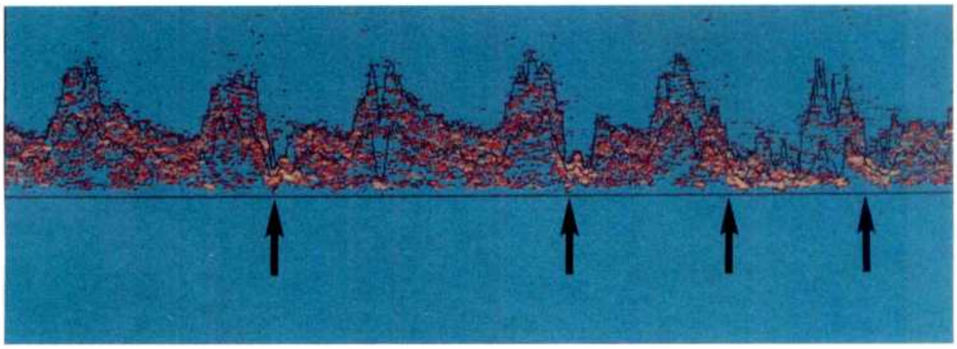

Figure 1 *Discrete emboli following presumed displacement of air from the T limb of a Pruitt–Inahara shunt (patient 2). The emboli appear as transient high-energy signals superimposed on the middle cerebral artery waveform (arrows)*

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Abdominal aortic aneurysm in the elderly

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Thirty-five patients over the age of 80 years underwent surgery for abdominal aortic aneurysm between January 1985 and December 1990. Of these, 25 had surgery for ruptured aneurysm (mortality rate 56 per cent) and ten had surgery for symptomatic or asymptomatic aneurysm (mortality rate zero). The mortality rate for patients with rupture aged over 80 years was considerably greater than that for those under 80 years of age (56 versus *36 per cent). The mortality rate in the elderly population was zero for elective surgery but in those under 80 years it was 5 per cent. During the study period a prospective analysis of all referrals with aortic aneurysm was carried out, whether or not they underwent surgery and whether or not they were admitted to hospital. The ratio of patients accepted for operation to those not accepted for operation was 92:59 (1·56:1) in the under 80-year-old age group and 12:34 (0·35:1) in those aged over 80 years.*

There is an increasing number of elderly people in the population and an increasing incidence both of abdominal aortic aneurysm (AAA)[1,2] and the number of patients with aneurysm coming to the attention of the medical profession[3]. The decision whether or not to operate on an elderly person with an aneurysm therefore confronts the vascular surgeon more frequently. Several authors have stated that physiological, rather than chronological, age should be a major factor in the selection of patients for aortic surgery[4–8]. The report of the Confidential Enquiry into Perioperative Deaths[9] of 1987, however, suggested that patients over 80 years old with ruptured aortic aneurysm were unlikely to survive surgery and should not be operated on. The present study reviewed the experience of surgery for aortic aneurysm in the elderly in Edinburgh. The Edinburgh vascular surgical service carries out virtually all operations for ruptured aneurysm in the Lothian, Borders and the southern half of Fife Regions (a population of 1·2 million) and is therefore in a position to assess numbers of patients having surgery, and numbers being referred and being refused operation.

Patients and methods

Every patient over the age of 80 years who had undergone surgery for AAA between January 1985 and December 1990 was identified using the Lothian Surgical Audit database. Age at operation, sex, relevant past medical history, operative details, whether the surgery was for ruptured, symptomatic or asymptomatic aneurysm, intraoperative death and its cause, number of days spent in the intensive care unit, length of hospital stay and postoperative death were noted. Survival after discharge from hospital was obtained and an estimate of quality of life made by ascertaining the degree of independence and mobility.

To put the operative experience into context, a prospective study of all patients presenting to the vascular surgical service with an aneurysm (emergency or elective) but turned down for operation in the calendar year 1989 was carried out. This study included patients admitted to hospital who did not undergo surgery and all those notified to the vascular service by hospitals or general practitioners who were discussed by telephone and not transferred or who died during transfer.

Results

In the 6-year period studied, 35 of the 546 aneurysm operations carried out were in patients aged 80 years or over. There were 25 men and ten women with a median age of 81·5 (range 80–85) years. Ten patients underwent elective surgery for an asymptomatic or symptomatic aneurysm and 25 had immediate surgery for a ruptured aneurysm. All operations were carried out by a consultant vascular surgeon or by a senior registrar with consultant supervision.

All ten patients operated on electively survived surgery; five tube and five bifurcation grafts were inserted. No patient required intensive care management after operation. The median hospital stay was 18 (range 13–29) days. Seven of these patients are still alive, living at home or with relatives, and have reasonable mobility.

Seven of the 25 patients who had a ruptured aneurysm died during surgery, three from myocardial infarction and four from uncontrollable haemorrhage. A further seven died in the 30-day period after operation, three from multisystem failure, three from cerebrovascular accidents and one from myocardial infarction. The total 30-day mortality rate was therefore 56 per cent. In the 18 patients who survived operation, 13 tube grafts and five bifurcation grafts were inserted. The type of graft had no apparent influence on outcome as four of five patients receiving a bifurcation graft survived to discharge. Patients who survived to discharge spent a shorter time in the intensive care unit after operation than those who died (median (range) 2 (1–11) *versus* 4 (2–23) days). The median hospital stay for survivors was 15 (range 13–68) days. Six of the patients with a ruptured aneurysm are still alive. All live at home independently and are mobile; one person requires a walking stick.

As the numbers in both the ruptured and non-ruptured groups are relatively small, only a crude estimate of life expectancy after aneurysm surgery can be made. The median survival time for patients undergoing elective surgery who survived to discharge but subsequently died was 3 years 10 months (range 5 months to 5 years 6 months). For patients with ruptured aneurysm the median survival time was 3 years 8 months (range 3–5 years).

In the calendar year 1989, 104 aneurysm repairs (52 ruptured, 52 non-ruptured) were carried out and 93 patients were either deferred or turned down for operation. Of the latter group, 34 (37 per cent) were more than 80 years old (12 ruptured, 22 non-ruptured). Of those with rupture (mean age 86 years), the reason for being turned down for operation was recorded as age alone in two patients, and age and cardiac or respiratory or neurological status in nine; one patient refused operation. Only two of the 12 patients with aneurysm rupture had been seen previously by a vascular surgeon. Of those without rupture (mean age 83 years), the reason for being turned down for operation was given as age alone in six, age and cardiac status in four, age and neurological status in four,

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cardiac status alone in three, and disseminated or inoperable malignancy in four; one patient refused operation. During the same 1-year period, 12 aneurysms (nine ruptured, three non-ruptured) were surgically repaired in the over 80 years age group. The ratio of patients accepted for surgery to patients not accepted for surgery for those aged under 80 years was 92:59 (1·56:1); for the over 80-year-olds it was 12:34 (0·35:1).

Discussion

The results of the present series compare favourably with those of other authors, although quite a spectrum of outcome exists. Robson *et al.*[8] reported a series of 34 octogenarians undergoing surgery for aortic aneurysm which was categorized as 'emergency' or 'elective', with 20 in the former category and 14 in the latter. However, only 14 of the 'emergency' patients had ruptured aneurysm proven at operation and the operative mortality rate for emergencies of 35 per cent must not be confused with the mortality rate for rupture. The mortality rate for 'elective' cases was zero, as in the present series. Harris *et al.*[5] reported a 30-day mortality rate after operated ruptured aneurysm of 37 per cent in this age group and a mortality rate of 3 per cent for patients undergoing elective repair, but this included an operative mortality rate of 27 per cent for patients with symptomatic aneurysm. Treiman *et al.*[6] reviewed 8 years of operations on octogenarians with aortic aneurysm and found an overall operative mortality rate of 58·8 per cent after rupture and 8·6 per cent after elective surgery.

One feature that the present series has in common with most of the above is the high ratio of ruptured to non-ruptured aneurysms operated on; this is generally the case throughout Scotland[3]. This may occur because general practitioners and physicians do not refer elderly patients with aneurysm for surgical assessment, assuming that advanced age is a contra-indication to surgery[10]. A majority of the elderly patients arriving at hospital with ruptured aortic aneurysm have never been previously diagnosed[11]. This has given rise to calls for national screening programmes, especially in high-risk groups[12–14]. The high ratio of ruptures to non-ruptures, 3:1 in the study year, may also be the product of surgical selection; nine of 31 patients with rupture but only three of 25 without rupture known to the vascular surgical service underwent operation in that year. There is understandably more pressure to operate on an aged patient with a life-threatening ruptured AAA than one with an asymptomatic aneurysm.

Elderly patients, especially those with compromised cardiac function, tolerate blood loss poorly, and advanced age itself has been shown to be associated with postoperative complications and death[15]. In the present series, age and medical factors were the reason for withholding surgery in all but eight of the 34 patients not operated on. What should the policy be for surgical intervention in the patient presenting with a ruptured aneurysm who has already been turned down for elective surgery on medical grounds? Sterpetti *et al.*[16] advised operation on all such patients, accepting that the mortality rate is high. Ruckley[17] argued that the elderly patient with a ruptured aneurysm who arrives at hospital severely shocked or comatose is highly unlikely to survive surgery and should not be operated on. Clearly an agreed policy to suit everyone is not possible, and some selection is desirable if the financial and emotional toll (to patients, relatives, surgeons and nursing staff) is not to be too great. While the elective group may represent a highly selected population, the results show that choosing patients carefully does give a good operative outcome and quality of life after surgery. The opportunity for elective selection should be more frequently available. It is widely accepted for younger age groups that it is desirable to reduce the number of operations performed for ruptured aneurysm. The same should obtain in the elderly, and perhaps all patients with aortic aneurysm should be referred for specialist assessment, regardless of age.

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Systemic leakage during isolated limb perfusion for melanoma

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A hazard of regional perfusion for melanoma is incomplete isolation, resulting in leakage of the cytostatic drug into the systemic circulation. Data were analysed retrospectively on 438 melphalan perfusions performed for melanoma of the extremities during the period 1978–1990; continuous isotopic measurement of systemic leakage was carried out. The cumulative systemic leakage after 60 min perfusion was 0·9 per cent (95 per cent confidence interval 0·7–1·1 per cent). Systemic leakage of ≥ 1 per cent was detected in 12·6 per cent of perfusions, ≥ 5 per cent in 6·2 per cent and ≥ 10 per cent in 1·4 per cent. In 2·3 per cent of patients, systemic side-effects in the form of mild transient bone marrow depression occurred. Six variables related to the perfusion technique were assessed by multivariate analysis for their influence on systemic leakage. The level of isolation and diameter of the venous cannula emerged as significant factors. In addition, ligation of the internal iliac vein provided optimal isolation during iliac perfusion.

Regional isolated perfusion, introduced by Creech *et al.*[1] in 1958, is frequently used in the treatment of recurrent melanoma of the extremities[2]. Its main advantage is that a high dose of cytostatic drug (usually melphalan) can be given locoregionally, thereby avoiding systemic side-effects[3]. However, complete isolation of the limb is not always possible because of anatomical variation and for technical reasons; systemic leakage therefore sometimes cannot be prevented. In most perfusion centres, control of systemic leakage is carried out using an isotope technique. In the literature, systemic leakage at the end of melphalan perfusion has been reported to be as high as 30 per cent, producing systemic complications (including bone marrow depression) in 2–17 per cent of patients[4–9]. Recently, biological response modifiers such as recombinant tumour necrosis factor (rTNF) α have become available for high-dose regional administration[10]. Because the pharmacokinetic behaviour of these agents is different from that of melphalan and because their systemic toxicity can be severe, a proper isolation technique is even more crucial. Before embarking on perfusion with such agents, past experience of systemic leakage was evaluated. Particular attention was paid to six variables that might influence leakage.

Patients and methods

A total of 499 perfusions in 431 patients with melanoma were performed in the period 1978–1990. A database containing patient, tumour and treatment characteristics was used to acquire information on perfusions during which control of systemic leakage was carried out. Perfusions were divided into two groups: those resulting in systemic leakage of < 1 per cent and those resulting in leakage of ≥ 1 per cent.

The perfusion technique has been described in detail elsewhere[3]. Melphalan was generally given in a dose of 10 mg per litre of tissue for lower-extremity perfusion and 13 mg/l for upper-limb perfusion[11]. Tissue temperature during perfusion was usually 'controlled' normothermic (37–38°C) or, when performed within the framework of the European Organization for Research and Treatment of Cancer–World Health Organization (WHO) protocol for stage I melanoma, 'mild' hyperthermic (39–40°C). A few patients were perfused experimentally using 'borderline' hyperthermia (41–42°C)[12]. Perfusion was carried out with isolation at the axillary, brachial, iliac or femoropopliteal level. For iliac perfusion the internal iliac vein was routinely ligated, except for patients treated in The Netherlands Cancer Institute where this step was abandoned in 1986. To obtain the proximal (axillary or iliac) isolation level, a pin was inserted into the head of the humerus or iliac crest; an occluding rubber bandage was fixed around the pin and twisted around the root of the extremity. This technique prevented collateral circulation in subcutaneous tissue and muscle. To obtain the distal (brachial or femoropopliteal) isolation level, an inflating tourniquet was used. During limb isolation there was a dynamic balance between two pressure compartments, the systemic vasculature and the isolated circuit. The pressure of the former compartment could be influenced by adjusting the systemic blood pressure, while that of the latter was affected by alterations in extracorporeal flow rate.

Any leakage into the systemic circulation was monitored using a radioactive tracer. A small calibration dose of human serum albumin radiolabelled with ^{99m}Tc or ^{131}I was injected into the systemic circulation and a higher dose of the same isotope into the isolated extremity. Continuous monitoring was performed with a precordial scintillation probe. Systemic leakage was expressed quantitatively as a percentage such that 100 per cent leakage represented homogeneous distribution of the isotope in the body[13]. In this model it was assumed that the volumes of the extracorporeal circuit and the systemic vasculature are in the proportion 1:5. The priming volume of the extracorporeal circuit was about 750 ml and was composed of whole blood diluted with plasma expander to a haematocrit of around 30 per cent. The venous pressure in the isolated limb was monitored in the saphenous vein at the ankle. The perfusion procedure was flow-regulated; in the authors' practice the optimal flow rate is considered to be that which gives the highest possible flow without systemic leakage and with an increase in venous pressure of ≤ 10 cmH$_2$O from that at the start of perfusion. Physiological blood gas values are aimed for and a minimal flow rate of 40 ml per min per litre of perfused tissue has generally been found to be optimal[3].

To obtain the relationship between perfusion technique-related factors and systemic leakage, logistic regression analysis was performed using BMDP software (BMDP Statistical Software, Los Angeles, California, USA). The variables examined were: level of isolation, method of occlusion of collateral circulation (rubber bandage or inflating tourniquet), flow-rate adjustment, mean venous pressure of the isolated limb, mean systemic blood pressure and diameter of the venous cannula. The flow-rate adjustment was the necessary decrease or increase in perfusion flow rate according to venous pressure, systemic leakage or blood gas levels during perfusion. Venous pressure and systemic blood pressure were recorded as the mean of the values measured at 0, 30 and 60 min of perfusion. The diameter of the venous cannula determines the resistance to venous outflow[11]. For isolation at the iliac level, the factor of internal iliac vein ligation was also included in the analysis.

Results

Data were obtained on 438 perfusions carried out in 383 patients comprising 281 women and 102 men of mean age 54 (range 17–83) years. Of these, 124 patients were perfused for primary melanoma and 259 for recurrent melanoma of the

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extremities. The mean isotopically measured cumulative systemic leakage after 60 min perfusion was 0·9 per cent (95 per cent confidence interval 0·7–1·1 per cent). Systemic leakage was <1 per cent in 383 perfusions (87·4 per cent) and $\geqslant 1$ per cent in 55 (12·6 per cent). In the latter group, 27 perfusions (6·2 per cent) led to systemic leakage of $\geqslant 5$ per cent and six (1·4 per cent) of $\geqslant 10$ per cent. At 5–10 min after restoration of normal circulation, there was a mean release of isotope from the isolated extremity to the systemic circulation of 4·2 per cent (95 per cent confidence interval 3·9–4·5 per cent). In ten cases (2·3 per cent), systemic leakage (of $\geqslant 5$ per cent) resulted in a moderate bone marrow depression (grade II according to WHO criteria).

Table 1 shows perfusion variables in relation to systemic leakage. With respect to the level of isolation, brachial perfusions were excluded from the analysis because of their small number (nine). With univariate analysis (step 0 in *Table 2*), level of isolation ($P = 0{\cdot}0001$), diameter of the venous cannula ($P = 0{\cdot}011$) and flow-rate adjustment ($P = 0{\cdot}011$) all appeared to be significantly related to systemic leakage. There was also a highly significant difference in systemic leakage between iliac perfusion with and without internal iliac vein ligation. *Table 1* shows that 29 per cent of patients without ligation had $\geqslant 1$ per cent leakage as opposed to 10 per cent of those with ligation. With multivariate analysis, the level of isolation ($P = 0{\cdot}0003$) and diameter of the venous cannula ($P = 0{\cdot}011$) retained their significant predictive value (*Table 2*).

Table 1 *Variables related to perfusion technique tested as prognostic factors for systemic leakage*

	No. of perfusions	No. with leakage $\geqslant 1$%
Level of isolation		
Axillary	50	3 (6)
Iliac (ligation)*	227	23 (10)
Iliac (no ligation)†	69	20 (29)
Femoropopliteal	83	7 (8)
Collateral occlusion method		
Bandage	346	46 (13)
Tourniquet	92	9 (10)
Flow-rate adjustment		
Decrease	46	12 (26)
Constant	336	34 (10)
Increase	45	8 (18)
Unknown	11	
Mean venous pressure relative to start of perfusion (cmH$_2$O)		
$\leqslant 10$	352	40 (11)
>10	47	10 (21)
Unknown	39	
Mean systemic blood pressure (mmHg)		
$\leqslant 99$	18	3 (17)
100–139	319	40 (13)
$\geqslant 140$	84	9 (11)
Unknown	17	
Diameter of venous cannula (mm)		
$\leqslant 2{\cdot}99$	57	8 (14)
3·00–4·99	253	40 (16)
$\geqslant 5{\cdot}00$	113	6 (5)
Unknown	15	

Values in parentheses are percentages. *Internal iliac vein routinely ligated; †internal iliac vein not routinely ligated. *P* values are given in step 0 of *Table 2*

Table 2 *Logistic regression analysis of correlation between variables related to perfusion technique and systemic leakage*

	P		
	Step 0	Step 1	Step 2
Level of isolation	0·0001	0·0001	0·0003
Collateral occlusion method	0·35	0·99	0·99
Flow-rate adjustment	0·011	0·031	0·053
Mean venous pressure	0·072	0·047	0·059
Mean systemic blood pressure	0·65	0·99	0·84
Diameter of venous cannula	0·011	0·011	0·011

Step 1, controlled for level of isolation; step 2, controlled for level of isolation and diameter of venous cannula

Discussion

The mean cumulative systemic leakage of <1 per cent and the systemic complication rate, in the form of bone marrow depression, of <3 per cent are lower in the present series than in the literature, where leakage of up to 30 per cent[7,8] and an incidence of bone marrow depression ranging from 2 to 17 per cent[4–8] have been reported. This favourable outcome can probably be attributed to differences in perfusion technique and leakage detection method. With regard to technique, perfusion flow rate is an important factor. On the one hand, a flow rate is required that is sufficiently high to ensure physiological blood gas values in the limb while, on the other hand, it should not reach levels causing raised venous pressure, which may give rise to acute regional toxicity after perfusion[14] and systemic leakage[15]. For these reasons, the association of flow rate adjustment with leakage is not unexpected. Flow rates of about 40 ml per min per litre of perfused tissue, as used in the authors' practice, are probably optimal, although some have recommended higher rates[16]. With regard to the method for detecting leakage, we strongly advocate continuous isotope monitoring in preference to interval systemic blood sample control; the former allows flow rate to be adjusted directly according to systemic leakage[7,8].

Multivariate analysis showed that the level of isolation and diameter of the venous cannula were significant prognostic factors related to systemic leakage. Patients treated at the iliac level without ligation of the internal iliac vein had the highest leakage. The difference in systemic leakage between iliac perfusion with and without ligation of the internal iliac vein has also been highlighted in another study, which even advocated temporary occlusion of the common iliac vein to ensure optimal isolation[17]. However, in that study rather high cumulative leakage rates (using ^{125}I-radiolabelled human serum albumin) were reported after both ligation of the internal iliac vein (28 per cent) and occlusion of the common iliac vein (9 per cent). Temporary occlusion of the common iliac vein seems particularly appropriate in reperfusion, at which ligation of the internal iliac vein is sometimes difficult. With respect to leg perfusion, patients in the present study treated with isolation at the femoropopliteal level had the lowest systemic leakage. This may be because of the reliable compression of the inflating tourniquet used for this level, resulting in occlusion of the collateral circulation in subcutaneous tissue and muscle. The beneficial effect of a large venous cannula diameter can be attributed to a lower venous outflow resistance, lower venous pressure and, consequently, a higher flow rate.

When melphalan is given in a single dose at the start of perfusion, as in the present study, its concentration in the perfusate declines rapidly during the early period of drug circulation; there is a 40–50 per cent decrease[18] in melphalan concentration in the perfusate after 10 min and after 30 min of perfusion almost all the cytostatic agent has accumulated in the tissues. This is in contrast to the pharmacokinetic properties of rTNF-α, which has recently been introduced into perfusion methodology. The concentration of this agent remains constant in the perfusate throughout the 90 min of perfusion[10]. Furthermore, in contrast to melphalan, severe acute side-effects have been caused by far lower percentage systemic leakage of rTNF-α. Systemic peak concentrations of both melphalan and rTNF-α have been observed after perfusion when normal circulation was restored[19]. Also, in the present series the highest proportion of systemic isotope (4·2 per cent) was detected after restoration of the normal circulation. Systemic drug levels may derive from vascular components of the extremity or via release of drug from tissue-binding sites; it is possible that the latter plays a role in rTNF-α perfusion.

Clearly it is important that several issues regarding systemic leakage be considered. First, in perfusion of melphalan, control of systemic leakage is of major importance only during the first 30 min of perfusion, whereas with rTNF-α it is essential throughout the entire perfusion period. Second, after detection of systemic leakage during rTNF-α treatment, one should seriously consider discontinuing perfusion. Third, wash-out should be more thorough after rTNF-α than after melphalan perfusion.

In conclusion, flow- and venous pressure-controlled perfusion can result in a low cumulative systemic leakage as measured isotopically. This method, therefore, seems to be adequate for perfusion using rTNF-α, when potential systemic leakage must be avoided to prevent severe side-effects. To optimize isolation, ligation of the internal iliac vein in iliac perfusion procedures should be considered. In addition, a venous cannula with a large diameter should be used whenever possible.

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Posterolateral neck dissection: technique and results

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Posterolateral neck dissection, alone or combined with a modified radical neck dissection, may be an appropriate method of treating occult and clinically manifest nodal metastases of malignant epithelial tumours of the skin of the posterior scalp. The technique and results are described in 21 patients treated between February 1981 and November 1989. Transformation of nodal status from cN_0 to pN_+ was seen in five of 13 patients treated electively, who may benefit from such a procedure. During a mean follow-up of 47 months the disease was controlled locally in all patients. Three patients suffered regional recurrence of whom only one had a nodal recurrence within the region previously operated on. The results of this limited retrospective study confirm the value of posterolateral neck dissection in posterior scalp lesions.

Spread to regional lymph nodes occurs infrequently in patients with malignant epithelial tumours of the skin of the head and neck. These tumours fortunately show a predictable pattern of metastases within the nodal region[1]. Lymph node dissection for anterior scalp and ear lesions should therefore contain the preauricular, parotid and jugulodigastric nodes. Malignant epithelial tumours, such as invasive melanoma or squamous cell carcinoma of the scalp and nape of the neck, posterior to a coronal plane through the outer ear canals usually metastasize through the retroauricular and suboccipital nodes to the spinal accessory and upper part of the internal jugular chains (*Figure 1*). Only by a posterolateral neck dissection can occult and clinically manifest lymph node metastases in this region be adequately removed.

This type of neck dissection consists of comprehensive removal of all lymph node-bearing tissue of the retroauricular and suboccipital region in continuity with the contents of the posterior triangle of the neck and internal jugular chain. The operation is usually performed as an *en bloc* procedure with excision of the primary tumour[2-6].

This paper presents the results of this operation and discusses its rationale.

Patients and methods

Surgical technique

The technique for posterolateral neck dissection has been described previously[6] and is based on the description of Rochlin[2]. The spinal accessory nerve, jugular vein, splenius capitis and sternocleidomastoid muscle are preserved. Depending on the site of the primary lesion the operation is performed unilaterally or bilaterally.

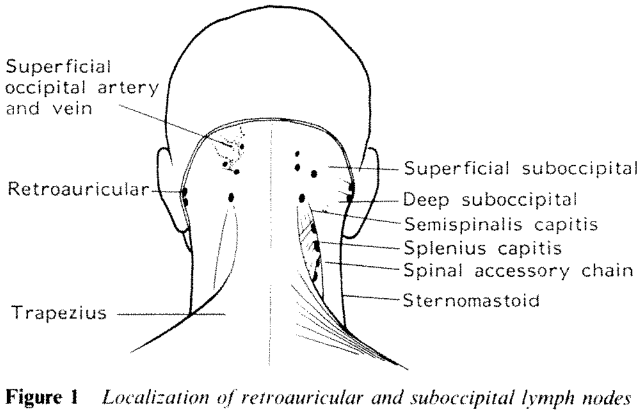

Figure 1 *Localization of retroauricular and suboccipital lymph nodes*

Curved skin incisions are made, extending from a wide local (re)-excision of the primary lesion to the anterior border of the lower part of the sternocleidomastoid muscle. If a concomitant parotidectomy is necessary, as for lesions near or of the ear, a preauricular incision is added with a 90° angle to the vertical part of the incision. Skin flaps are elevated to the midline of the posterior neck to the level of C3-C4, the clavicle and the anterior border of the sternocleidomastoid muscle.

The dissection begins with removal of the fibrofatty tissue and the retroauricular and suboccipital nodes along the occipital artery, which has to be sacrificed. The trapezius muscle is separated from the superior nuchal line up to C3-C4, and the upper portion transected cranial to the entry of the accessory nerve. By retracting the splenius muscle anteriorly it is possible to remove the deep lymph node-bearing tissue in the suboccipital region. The sternocleidomastoid muscle is retracted anteriorly and the dissection carried along the upper portion of the jugular chain including the subdigastric lymph nodes, with preservation of the spinal accessory nerve.

A modified radical neck dissection is carried out when peroperative frozen-section examination of the subdigastric lymph nodes is positive. A split-thickness skin graft is usually necessary to cover the defect at the site of the primary lesion.

Patients

Between February 1981 and November 1989, posterolateral neck dissection was used to treat 21 patients whose clinical characteristics are summarized in *Table 1*. There were 15 men and six women with a mean age of 46 (range 29-69) years. The procedure was therapeutic in eight patients with clinically positive regional lymph nodes. One of these patients had a squamous cell carcinoma of the occipital skin, another a Merkel cell tumour of the pinna and six invasive cutaneous melanoma. An elective operation was performed 'in continuity' in the remaining 13 patients. The criteria for elective regional node dissection were intermediate- and high-risk primary cutaneous melanoma without palpable cervical lymph nodes (stage I, M. D. Anderson Cancer Center classification), with a Breslow thickness $\geq 1 \cdot 0$ mm (seven patients) or any local recurrence or satellitosis within 3 cm of the primary site (stage II) (six patients). The anatomical site of the primary lesions is shown in *Table 1*.

A unilateral procedure was performed in 15 patients, of whom 13 had a primary invasive cutaneous melanoma. Six patients underwent a bilateral procedure as the primary melanoma was located close to the midline of the scalp and neck. All dissections, with the exception of that in the patient with the Merkel cell tumour, were performed in continuity with a wide excision of the primary tumour area. This excision was never <2 cm from the tumour margins or the area of satellite nodules in patients with melanoma. In five patients the procedure had to be extended to a modified radical neck dissection because subdigastric or jugular nodes were positive on frozen-section examination (*Table 2*). In four patients concomitant subtotal parotidectomy was carried out. Owing to the location and extent of the primary melanoma, ear amputation was necessary in two patients.

Local recurrence was defined as any relapse occurring within an area 3 cm from the scar or skin graft. Regional recurrence was divided into nodal and non-nodal relapse, i.e. in-transit or subcutaneous metastases.

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All patients were observed at regular follow-up visits. The median duration of follow-up was 28 (mean 47; range 9–129) months. The evaluation of patients was ended in January 1992.

Results

There was no postoperative mortality and only minimal morbidity (wound infection, one; partial necrosis of the split skin graft, one). The accessory nerve had to be sacrificed for oncological reasons in two patients. In the remaining patients shoulder function was not impaired. In five of the 13 patients who underwent an elective operation after clinical staging (cN$_0$), histological examination revealed positive nodes (pN$_+$). Two of these patients had microscopically involved nodes at various levels, suboccipital and dorsal, without extranodal disease. Resected specimens showed nodal involvement in all of the eight patients who underwent therapeutic dissection. In five of these patients nodal involvement occurred on more levels than was apparent clinically, two with extranodal spread (*Table 2*). There was no local recurrence at the primary site.

Table 1 *Patient details*

No. of patients	21
Mean (range) age (years)	46 (29–69)
Sex ratio (M:F)	15:6
Indication	
Melanoma	
cN$_+$	6
cN$_0$	13
Squamous cell carcinoma	
Occipital cN$_+$	1
Merkel cell carcinoma	
Pinna cN$_+$	1
Location of primary tumour	
(Sub)occipital	9
Retroauricular	8
Parieto-occipital	4

Table 2 *Pathology*

		Positive nodes	
	No. of patients	Location	Total no. involved
Therapeutic group (n = 8)			
Squamous cell carcinoma	1	Suboccipital	2
Merkel cell carcinoma	1	Suboccipital	1
		Retroauricular	1
		Subdigastric	1
Melanoma	6	Suboccipital	3
		Dorsal	4
		Subdigastric	4
Elective group (n = 13)			
Melanoma			
pN$_0$	8	—	—
pN$_+$	5	Suboccipital	2
		Dorsal	5

Three of the 21 patients suffered regional recurrence. As six bilateral procedures had been carried out, there were 27 neck areas at risk after surgery, and regional failure was recorded in three of the neck regions during follow-up. One of these patients had clinically palpable regional lymph node metastases from a melanoma (stage IIIB); the other two presented with stage I or II melanoma. Only one of these patients had true regional nodal recurrence within the operative area. This patient had undergone elective dissection for a nodular melanoma, 2·8 mm thick, and ulceration. After 13 months he had nodal recurrence in the area previously operated on. Distant metastases were detected 3 years after a subsequent modified neck dissection had been performed. The other two patients developed recurrence outside the previous operative region. Both had synchronous distant metastases. One of these patients developed a subcutaneous recurrence outside the surgically treated field 2 months after a bilateral elective procedure for a primary nodular melanoma with ulceration and Breslow thickness of 5·6 mm. At 1 year he died from distant metastases. A therapeutic dissection was carried out in the other patient for a superficial melanoma, 0·9 mm thick with satellitosis and regional node involvement. At 18 months after this operation lymph node metastasis was observed beyond the dissected field. In the 13 patients (eight therapeutic, five elective) with pathologically proven lymph node metastases, there was only one regional failure.

The mean disease-free survival time for the whole group was 38 (median 24; range 2–129) months, and for patients with a primary cutaneous melanoma it was 31 months. In the elective and therapeutic dissection groups, disease-free survival for patients with melanoma was 36 and 19 months respectively.

The mean survival time of all patients was 47 (median 45; range 9–129) months. In patients with cutaneous melanoma it was 42 months overall, and 46 and 32 months respectively for elective *versus* therapeutic operation.

Seven patients, five with melanoma of the skin, were without evidence of disease, the latter five after a mean follow-up of 56 months (*Table 3*). Of the 11 patients with melanoma and pathologically positive nodes, two are still alive with disease after 78 and 87 months. Ten of these 11 patients had two or more involved nodes.

All patients with stage IIIB melanoma and eight of the 13 without clinically palpable pathological lymph nodes (cN$_0$) developed distant metastases. Three patients with nodes that were found to be negative after dissection developed distant metastases. Regional failure occurred in one patient after 13 months. In patients with pathologically positive nodes, however, regional failure occurred in two patients after a mean of 10 months.

Ten patients died from distant metastases within a median of 23 months. Seven patients had cerebral metastases, six had

Table 3 *Survival according to histology, clinical stage and type of lymphadenectomy*

		No evidence of disease		Recurrence	
Histology	Type of lymphadenectomy	No. of patients	Mean survival (months)	No. of patients	Mean survival (months)
Non-melanoma					
Squamous cell carcinoma	Therapeutic	1	129	—	—
Merkel cell carcinoma	Therapeutic	1	70	—	—
Melanoma					
Stage I or II	Elective	5	56	8	40
Stage IIIB	Therapeutic	0	0	6	32

pulmonary metastases and two had hepatic metastases. Four patients are still alive with disease after 92, 87, 78 and 45 months.

Discussion

Radical and modified radical neck dissection remains the treatment of choice[7] in the management of cervical metastases at level I through V, but retroauricular and suboccipital lymph node metastases from malignant epithelial tumours of the posterior scalp cannot be removed adequately by standard radical neck dissection[6–9]. In these patients, unilateral or bilateral posterolateral neck dissection should be performed as first described by Rochlin[2], who removed the upper part of the trapezius muscle. Others had a more radical approach with resection of the splenius and sternocleidomastoid muscle for better dissection of the deep suboccipital nodes[2].

Together with the upper back and upper posterior arm, the skin of the nape of the neck and scalp belong to the so-called BANS (back–arm–neck–scalp) region. Due to the rich network of intradermal lymphatics, melanoma originating in the scalp appears to behave more aggressively than that from a non-BANS area[10–12]. Besides a higher frequency of nodular type and ulceration, this detrimental effect on prognosis may also be explained by the fact that these scalp lesions are detected late and at a more advanced stage because of the overlying hair. About 20 per cent of patients with scalp and neck melanoma develop regional lymph node metastases within 2 years and 20–40 per cent of those with head and neck melanoma and clinically negative nodes appear to have microscopic metastases[13–15].

The 5-year survival rate appears to improve when these microscopically positive nodes have been removed electively, and several authors have strongly endorsed wide excision *en bloc* with elective regional node dissection in patients with clinically localized (stages I and II) melanoma[16–19]. Although some multifactorial analyses have shown significant survival benefit in patients with superficial spreading and nodular melanoma, others have detected no survival advantage[20,21]. This controversy will remain in the absence of a prospective randomized study of patients with head and neck melanoma. Adequate removal of microscopic disease seems to be the optimal treatment in patients with primary melanoma[22,23].

This study has shown that accurate preoperative identification of lymph node metastases in this region by palpation alone is insufficient. Five of the 13 patients operated on electively had histologically proven nodal conversion (cN_0 to pN_+). Three of these patients had multiple microscopic nodal foci. Owing to the overlying muscles it is difficult to assess clinically the absence of regional metastatic disease in this area. After posterolateral neck dissection for melanoma of the posterior scalp, regional recurrence occurred in three of the 27 areas at risk, a rate that is in accordance with the literature[24–26]. Only one patient treated unilaterally developed a nodal recurrence within the dissected area. The morbidity of the operation is low and elective dissection is recommended in those with a posterior scalp melanoma $\geqslant 1{\cdot}0$ mm thick or a stage II lesion. This strategy is defensible as therapeutic dissection of pathologically involved nodes in patients with stage II disease is associated with subsequent recurrence in up to 50 per cent of cases[8].

Whether the early detection of clinically occult regional node involvement will lead to an improved survival rate or better locoregional control remains to be proven in randomized studies. In patients without melanoma, posterolateral neck dissection seems to offer an optimal therapeutic effect in combination with postoperative radiotherapy when two or more lymph nodes are positive or in the case of extranodal disease. In patients with invasive cutaneous melanoma the prognosis was adversely affected in those with positive nodes, whether the neck dissection was elective (N_0) or therapeutic (N_+).

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Staging of supratentorial hemispheric glioma using tumour extension, histopathological grade and extent of surgical resection

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A 'TGS' classification for supratentorial brain glioma is proposed, based on three parameters: tumour extension (T), histopathological grade (G) and extent of surgical resection (S). Two groups of patients were analysed: the first ($n = 137$) *had tumour submitted to stereotactic biopsy; the second* ($n = 60$) *had malignant glioma operated on by craniotomy and tumour resection. All three staging parameters significantly influenced survival. Histopathological grade was the most significant factor, and the only independent variable on multivariate analysis, followed by extent of tumour and then extent of surgical resection. The data support the applicability of the proposed parameters for a staging classification of hemispheric brain glioma.*

The staging of malignancy may aid the clinician in planning treatment and making a prognosis, assist in the evaluation of results of treatment and facilitate the exchange of information between centres[1,2]. The tumour node metastasis (TNM) classification is not readily applicable in neuro-oncology. Glioma is mainly a focal disease and over 90 per cent of patients with supratentorial malignant glioma die as a result of recurrence at the original site of the tumour[3,4]. Multicentric lesions account for no more than 6–8 per cent[5,6]; brain tumours usually do not metastasize, the incidence of distant spread of malignant glioma being <10 per cent.

For some tumours, such as soft tissue sarcoma[7], the anatomical extent of the disease is evaluated in association with other tumour characteristics to achieve a clear definition of stage; this may also be possible with brain tumours. Early lesions submitted to a more complete removal and more substantial mass reduction are probably associated with better survival rates. The extent of surgery may be considered an important factor in staging[8]; extent of resection is a useful marker for tumours such as neuroblastoma and nephroblastoma[1,2].

The following parameters were therefore examined as markers for staging supratentorial glioma[9]: T (tumour extent; T_{1-3}), G (grading of anaplasia; G_{1-4}) and S (extent of surgical removal; S_{1-3}) (*Table 1*).

Patients and methods

A total of 197 patients (aged 18–71 years) treated between 1980 and 1988 were analysed. They were divided into two groups. Group 1 ($n = 137$) comprised patients undergoing stereotactic biopsy with multiple specimens collected stepwise at 5–10-mm intervals along the chosen tracks. Different parts of the tumour mass and surrounding brain tissue were analysed. In this group the extent of tumour, inferred from contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), was confirmed by analysis of specimens taken along the selected trajectories.

Group 2 ($n = 60$) comprised patients with malignant astrocytoma and glioblastoma undergoing surgical resection by craniotomy. After operation patients received conventional external radiotherapy (54–60 Gy in fractionated doses). Tumours in this group had a short natural history and better definition by use of neuroimaging techniques. Tumour extension was assessed by evaluating the maximum diameter of the enhanced area on postcontrast CT scan and, when available, on T1-weighted MRI following gadolinium–diethylenetriamine pentaacetic acid imaging[10]. Tumour grading was evaluated according to the World Health Organization (WHO) classification (1979). The term $G_{2/3}$ was used to indicate astrocytoma demonstrating focal anaplasia (tumour progression)[11], in which it was uncertain whether histological features were grade 2 or 3. The extent of surgical resection of tumour was verified using postoperative contrast-enhanced CT or MRI at 7–10 days and 1 month from operation.

Table 1 *Details of the categories of proposed staging system*

Tumour extent (cm)	
T_1	<3
T_2	3–5
T_3	>5
Grading of malignancy	
G_1	WHO I
G_2	WHO II
G_3	WHO III
G_4	WHO IV
Extent of surgical resection	
S_1	Gross total removal (tumorectomy)
S_2	Subtotal removal (residual disease <10 per cent)
S_3	Partial removal

WHO, World Health Organization

Survival estimates and actuarial curves were determined using Kaplan–Meier and Bergson–Gage methods. Differences between curves were assessed by the log rank test. Pearson's correlation coefficient (r) and the Cox proportional hazards regression model were used in a stepwise manner to determine the relative prognostic significance of the three variables tested (T, G and S).

Results

Details of patients according to TGS status are shown in *Tables 2* and *3*.

Group 1

T. The prognostic influence of tumour extension was evaluated within the most consistent and homogeneous histopathological group, glioblastoma (G_4) (*Figure 1*). The mean(s.e.m.) 1- and 2-year survival rate for T_2 glioblastoma was 17·6(9·2) and 5·9(5·7) per cent respectively, with a median survival time of 9 months. In contrast, the mean(s.e.m.) survival rate at 4 months for T_3 glioblastoma was 16·6(8·8) per cent dropping to zero by 1 year (median survival time 5 months).

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Table 2 *Details of patients undergoing stereotactic biopsy* (n = *137*)

	No.	T_1	T_2	T_3
Astrocytoma (n = 67)				
G_1	3	2	1	0
G_2	20	3	3	14
$G_{2/3}$	24	0	5	19
G_3	20	0	1	19
Oligodendroglioma (n = 27)				
G_2	25	1	13	11
G_3	2	0	0	2
Glioblastoma (n = 43)				
G_4	43	0	21	22

G. The influence of grade of malignancy on survival was assessed within the group with the most homogeneous T status, those with T_3 astrocytoma (*Figure 2*). In these tumours the mean(s.e.m.) actuarial survival rate for G_2 astrocytoma at 5 and 9 years was 85·7(13·2) and 57·1(21·7) per cent respectively,

Table 3 *Details of patients undergoing surgery* (n = *60*)

	T_1	T_2	T_3	S_1	S_2	S_3
Anaplastic astrocytoma (G_3; n = 23)	0	14	9	8	12	3
Glioblastoma (G_4; n = 37)	0	20	17	13	17	7

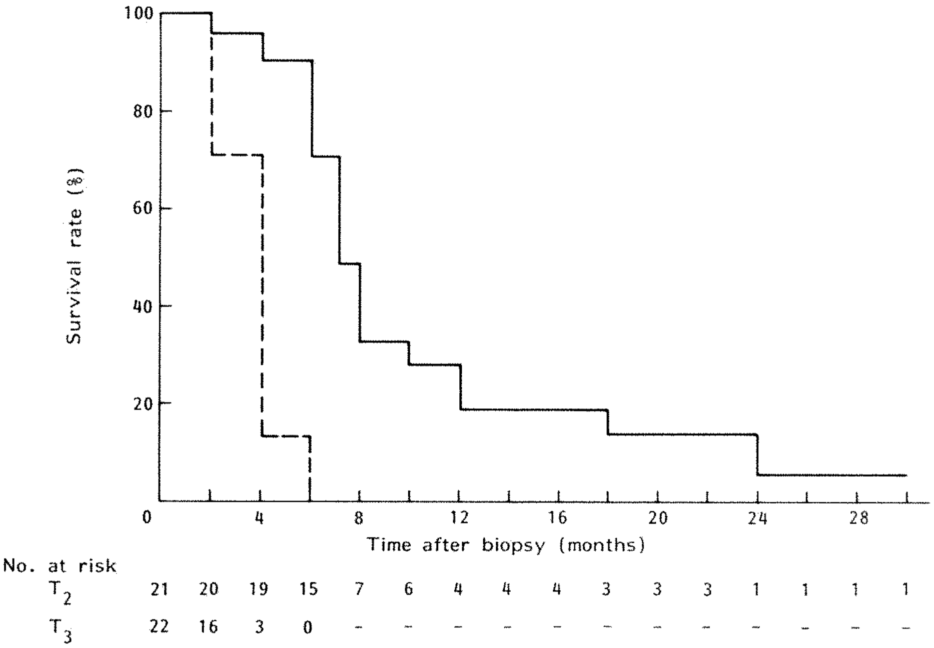


Figure 1 *Survival curves for 43 patients with glioblastoma, according to tumour extent.* ——, T_2 (n = *21*); - - -, T_3 (n = *22*). P < *0·0001* (*log rank test*)

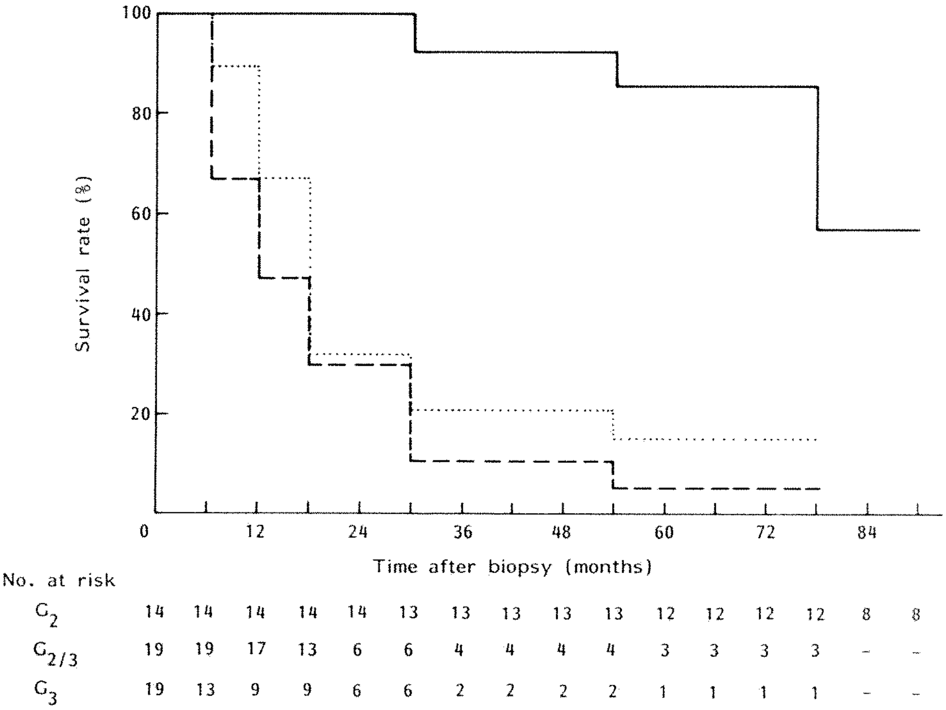
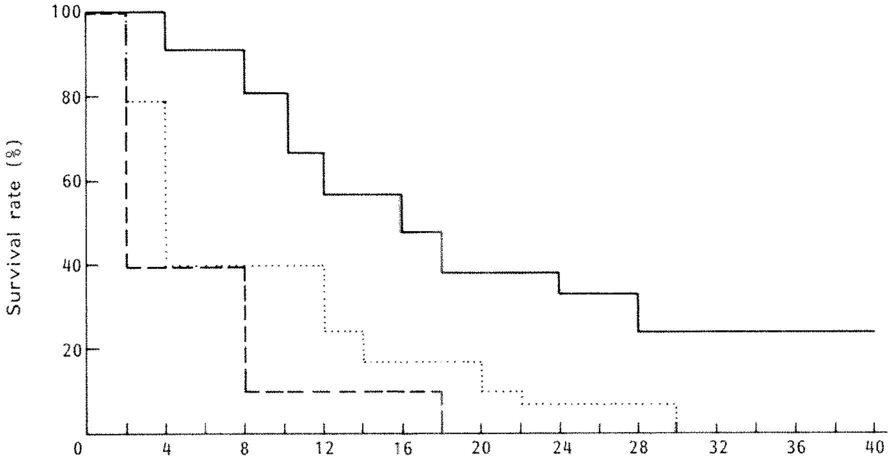


Figure 2 *Survival curves for 52 patients with astrocytoma of tumour extent T_3, according to histological grade of anaplasia.* ——, G_2 (n = *14*); ·····, $G_{2/3}$ (n = *19*); - - -, G_3 (n = *19*). P < *0·003* (*log rank test*)



No. at risk																					
S_1	21	21	21	21	20	19	17	14	13	12	10	9	8	8	7	7	5	5	5	5	5
S_2	29	29	27	23	20	17	14	11	7	5	5	5	3	2	1	-	-	-	-	-	
S_3	10	10	8	4	4	4	1	1	1	-	-	-	-	-	-	-	-	-	-	-	-

Figure 3 *Survival curves for 60 patients with malignant glioma, according to extent of surgical resection.* ——, S_1 (n = *21*); ·····, S_2 (n = *29*); – – –, S_3 (n = *10*). P < *0·0002* (*log rank test*)

with a median survival time of 114 months. For G_3 astrocytoma, the mean(s.e.m.) cumulative survival rate at 2 and 5 years was 29·4(11·2) and 5·2(4·7) per cent respectively, with a median survival time of 13 months. The category $G_{2/3}$ showed a survival rate closer to G_3 than did G_2 astrocytoma (median survival time 22 months).

Group 2

S. The influence of the extent of surgical resection on survival was tested in malignant astrocytoma and glioblastoma. *Figure 3* shows survival rates for the whole series with respect to degree of tumour removal. The mean(s.e.m.) 1- and 2-year survival rates after gross total removal (S_1) were 69·1(11·2) and 38·0(10·0) per cent respectively (median survival time 20 months); after subtotal removal (S_2) the values were 38·2(9·2) and 7·0(6·3) per cent respectively (median survival time 12 months). Patients undergoing partial removal (S_3) showed a mean(s.e.m.) 1-year actuarial survival rate of 11·4(12·2) per cent, which dropped to zero at 18 months (median survival time 6 months). The median survival time for malignant astrocytoma alone was: S_1, 74 months; S_2, 16 months; and S_3, 6 months. For glioblastoma the S_1 group had a median survival time of 14 months, S_2 9 months and S_3 5 months.

Multivariate analysis of the whole series of 197 patients showed a hierarchy in the prognostic significance: G was the most influential and the only independent variable ($r = -0·05$ *versus* T, $r = 0·06$ *versus* S; $P = 0·0004$), followed by T ($P = 0·013$) and S ($P = 0·11$). This last parameter correlated with T ($r = 0·65$, $P = 0·01$); cutting off the masking effect of T, so S became significant ($P = 0·003$).

Discussion

Difficulties have been encountered in developing staging systems for tumours of the central nervous system. Attempts have been made to stage infratentorial tumours in children[12,13]. In 1985 Edwards and Klein[14] proposed a series of prognostic factors (TGSM), similar to those in the present paper, to stage hemispheric tumours. The prognostic importance of T, G and S was stressed by Kricheff *et al.*[15] in 1963. In 1987 the Union Internacional Contra la Cancrum[2], drawing on an American Joint Committee on Cancer proposal, suggested a TNM-like classification for brain tumours, utilizing the factors T, G and M. This is the only current system but its faults are[16]: the T parameter includes tumours assessed either by spatial extension (T_1 and T_2) or by location (T_3 and T_4) so that tumours <5 cm in size are not adequately specified; G should refer to the WHO classification of brain tumours and any reference to the amount of anaplasia is anachronistic; and the classification is not equally suitable for all intracranial tumours, some of which (such as meningioma and midline tumours) have peculiar characteristics.

The present paper represents an initial step to describe a staging system for cerebral hemispheric glioma. The following aspects can be outlined.

1. The results confirm the prognostic value of the controversial factor T. There was an ordering of tumour size, such that patients with lesser tumour extension had longer survival. The subdivision proposed was schematic and, in part, arbitrary, but proved to be of practical value and statistically significant.
2. The data confirm the relevance of G and the difficulty in assessing tumour grade in astrocytoma, due mainly to the heterogeneity of such tumours[11].
3. The results confirm the prognostic value of surgery, longer survival being associated with more extensive tumour resection.
4. T and S correlated in the multivariate analysis, as if surgical resection could replace the importance of tumour extension by reducing tumour mass.
5. Even if G is the most significant parameter, S and T heavily influence survival.

It is difficult to know whether this method of staging is suitable for hemispheric glioma. More patients and longer periods of observation are required for validation.

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Graves' ophthalmopathy after subtotal thyroidectomy and radioiodine therapy

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Forty-five patients with Graves' ophthalmopathy were studied prospectively. Twenty-one patients (42 orbits; group 1) were treated surgically by subtotal thyroidectomy and 24 (48 orbits; group 2) received radioiodine therapy. All patients underwent tests of thyroid function, ophthalmological examination, and axial and coronal computed tomography before and 12 months after treatment. Patients in group 1 showed significant improvement in the Feldon score ($P < 0\cdot001$)*, in proptosis as estimated by Hertel exophthalmometry* ($P < 0\cdot001$) *and in proptosis* ($P < 0\cdot001$)*, maximum diameter of the medial rectus* ($P < 0\cdot01$)*, lateral rectus* ($P < 0\cdot05$)*, superior group* ($P < 0\cdot05$) *and inferior rectus* ($P < 0\cdot001$) *muscles as estimated by computed tomography. Patients in group 2 showed significant improvement only in the Feldon score* ($P < 0\cdot05$)*. The ophthalmopathy of Graves' disease improves to a greater extent after subtotal thyroidectomy than after radioiodine therapy.*

The influence of thyroid surgery and radioiodine therapy on Graves' ophthalmopathy is controversial. Some contend that subtotal thyroidectomy exacerbates ophthalmopathy[1,2] and that ocular involvement could contraindicate surgery. Others have shown that neither treatment alters the course of Graves' ophthalmopathy[3–7].

Many studies have used inaccurate and subjective measures of little value[2,3,6], and disparate and short-term follow-up[7,8]. The present study used an objective measuring system to compare the effects of subtotal thyroidectomy and iodine-131 on Graves' ophthalmopathy by clinical and radiological evaluation of the orbit.

Patients and methods

Forty-five patients (90 orbits) with Graves' ophthalmopathy were studied. Twenty-one patients (42 orbits) were treated by subtotal thyroidectomy (group 1; six men and 15 women, mean age 32 (range 18–59) years) and 24 (48 orbits) with iodine-131 to a total dose of 5–20 mCi (group 2; eight men and 16 women, mean age 39 (range 22–65) years).

The choice of treatment was determined according to criteria published in the survey of medical strategies for the management of Graves' disease in Europe[9].

All patients underwent morphological and thyroid function tests, verification of smoking history, ophthalmological examination, ocular status categorization according to the American Thyroid Association classification[10] and were scored using the Feldon scale (evaluation of seven clinical signs: proptosis, lid retraction, lagophthalmos, vertical and horizontal oculomotor dysfunction, optic nerve involvement and periorbital oedema)[11,12]. They also underwent axial and coronal computed tomography (CT) before surgery or iodine-131 therapy, and 12 months after treatment.

Each patient received antithyroid drugs and β-blockers over a 1–3-year period from the onset of hyperthyroidism to the initiation of the prescribed treatment.

Paired and unpaired t tests were used, where appropriate, to compare the differences between various groups. $P < 0\cdot05$ was considered significant.

Radiology

A Somatom DR2-Siemens high-resolution scanner (Siemens, Munich, Germany) was used to perform the orbital scans.

CT was carried out with use of a 25-cm field of view, a 256-image matrix, a window width and level setting of 350 and 70 units respectively, and a magnification factor of 2·0. Measurements obtained directly from CT images were converted to true size using a scalimeter. Axial views were obtained parallel to the orbitomeatal line. Supine direct coronal images were obtained with variable angles to avoid dental amalgam or because of limitation in neck mobility. Ninety orbits were scanned with contiguous 2-mm thick sections.

Maximum horizontal diameters of the bellies of the medial and lateral rectus muscles were measured from axial scans. Maximum vertical diameters of the inferior rectus and superior muscle group (superior rectus and levator palpebrae superioris) were measured from direct coronal images.

The degree of proptosis was calculated by measuring the perpendicular distance from the anterior globe margin to the interzygomatic line on axial scans at the midglobe level.

Results

Clinical findings at 12 months based on the American Thyroid Association classification showed improvement in 34 orbits in group 1. Eight orbits remained unchanged and there was no instance of deterioration. In group 2 improvement was seen in eight orbits, no change in 28 and deterioration in 12 (*Figure 1*). The degree of proptosis estimated by Hertel exophthalmometry showed significant improvement in group 1 12 months after treatment ($P < 0\cdot001$). This was not seen in patients in group 2 (*Figure 2*).

The Feldon score indicated significant amelioration in both groups (group 1, $P < 0\cdot001$; group 2, $P < 0\cdot05$).

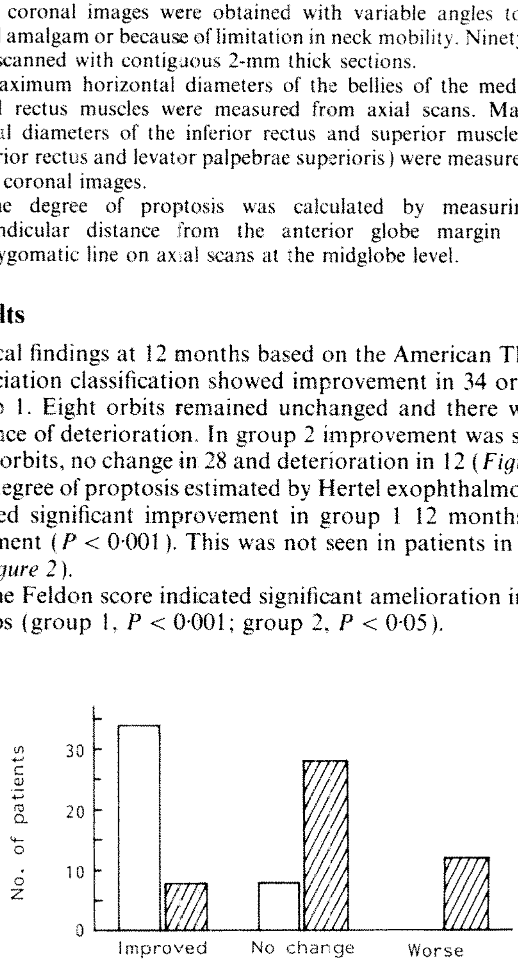

Figure 1 *Ophthalmopathy at 12 months after surgery* (□) *or radioiodine therapy* (▨)*, assessed using the ocular status classification of the American Thyroid Association*

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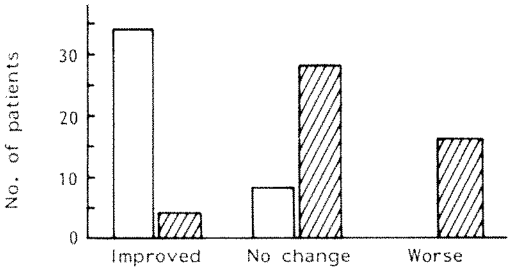

Figure 2 *Change in the degree of proptosis at 12 months after surgery (□) or radioiodine therapy (▨), assessed using Hertel exophthalmometry*

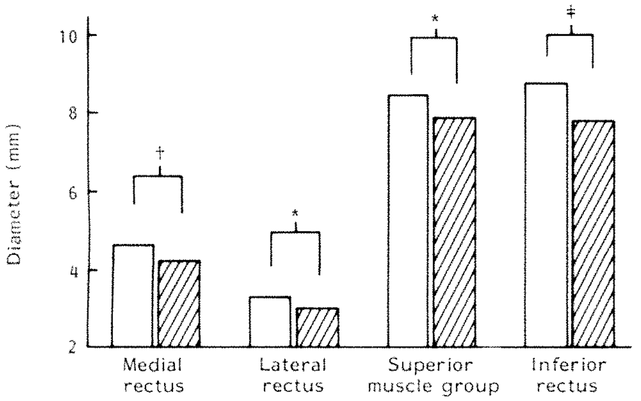

Figure 3 *Computed tomographic assessment of the mean maximum diameter of extraocular muscles in patients undergoing subtotal thyroidectomy, before (□) and 12 months after (▨) surgery.* *$P < 0{\cdot}05$; †$P < 0{\cdot}01$; ‡$P < 0{\cdot}001$ *(Student's paired* t *test)*

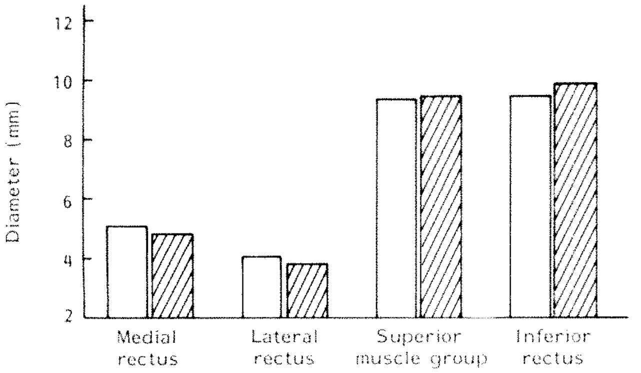

Figure 4 *Computed tomographic assessment of the mean maximum diameter of extraocular muscles in patients receiving radioiodine therapy, before (□) and 12 months after (▨) treatment. There were no statistically significant differences*

Results of the assessment of extraocular muscles and degree of proptosis by CT are shown in *Figures 3–5*. No significant improvement following treatment was seen in group 2 in the CT analysis.

Improvement in the degree of proptosis estimated by CT was significantly greater in group 1 than in group 2 12 months after treatment ($P < 0{\cdot}01$).

No correlation was found between change of ocular status and smoking history.

Thyroid status and replacement therapy at 12 months were as follows. In group 1, five patients became euthyroid without treatment and 16 euthyroid with L-thyroxine (three received 50 μg/day, ten 100 μg/day, three 150 μg/day). In group 2, four patients became euthyroid without treatment, one was hypothyroid with L-thyroxine (50 μg/day) and 19 remained hyperthyroid with thyroxine but became euthyroid with carbimazole or methimazole (three with low doses, 0–15 mg/day; 12 with medium doses, 16–30 mg/day; four with high doses, >30 mg/day).

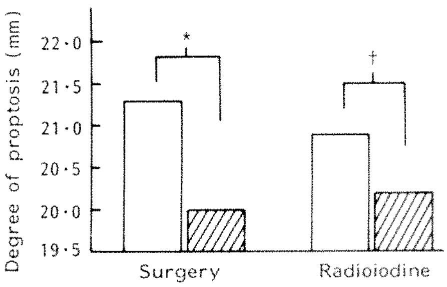

Figure 5 *Computed tomographic assessment of the mean degree of proptosis in the two groups of patients before (□) and 12 months after (▨) treatment.* *$P < 0{\cdot}001$; †P *not significant (Student's paired* t *test)*

Discussion

Since Naffziger[1] reported ocular exacerbation following thyroidectomy in one patient in 1931, others have described similar effects[2]. Evaluations have usually been based on the degree of proptosis estimated by Hertel exophthalmometry. Others have reported that thyroidectomy has no effect on the development of Graves' ophthalmopathy[3–7,13]. Similar controversy exists regarding the use of radioiodine therapy[5,6,13–16].

Various imaging techniques[7,11,12,17–19] allow objective evaluation of the course of Graves' ophthalmopathy. The latest CT scanners generate two-dimensional high-resolution images, making it possible to distinguish extraocular muscles, optic nerve, tear gland and bony orbit in axial and coronal sections.

The present study has shown a beneficial ocular response in patients undergoing surgery, with a decrease in the largest diameter of each of the extraocular muscles and in the degree of proptosis estimated by both CT and Hertel exophthalmometry.

Although patients receiving radioiodine therapy improved or remained unchanged, the amount of improvement was not significant, with the exception of the Feldon score. The dosage of radioiodine used to control hyperthyroidism has varied in the past few years, tending towards the use of ablative doses. However, as advised by Kendall-Taylor[13], repeated low doses are used by the present authors because hyperthyroidism should not be treated with an ablative dose of radioiodine if the patient has features of ophthalmopathy.

The present results indicate that neither therapy exacerbates ophthalmopathy and that subtotal thyroidectomy leads to significant improvement in the extraocular musculature. This is particularly so for both the medial and inferior rectus muscles, which are the two most affected in Graves' ophthalmopathy[17–19]. The Hertel exophthalmometer[7] is capable of producing results comparable to those estimated by CT in the evaluation of proptosis following treatment. Its advantages include easy use and minimal cost; its disadvantage is that it cannot be used to evaluate internal structures.

Surgical treatment produces improvement in Graves' ophthalmopathy. Longer term studies are required.

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Role of computed tomography in the staging of primary breast cancer

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The detection of metastases in patients presenting with primary breast cancer alters prognosis and may significantly affect management. The extent of evaluation before treatment, however, in patients with apparently localized disease remains controversial. Although medical history, physical examination, chest radiography, full blood count and liver function tests are considered important[1], imaging techniques such as bone and liver scintigraphy have a low yield in asymptomatic patients[2,3]. The value of computed tomography (CT) has not been established. This study examined whether CT enabled cost-effective detection of metastases in the management of these patients.

Patients and methods

A retrospective review of the findings and outcome of 117 patients with apparently localized breast cancer presenting between August 1988 and October 1991 was carried out. CT of the head, chest, abdomen and pelvis was performed within 3 months of definitive breast surgery using a Siemens Somatom DRH scanner (Siemens, Erlangen, Germany). Continuous sections from brain to pubic symphysis with dynamic mode and intravenous contrast were used and assessed on bone, lung and soft tissue windows. Reporting was by one of five consultant radiologists as part of the routine workload. Other investigations are shown in *Figure 1*. Most patients had disease of early tumour stage (T_1, 38; T_2, 51; T_3, 16; T_4, 12), and nodal involvement rose proportionately with increasing T stage. Follow-up ranged from 6 to 42 (median 20) months.

Results

The yield of the different staging investigations and their relative cost are shown in *Figure 1*. CT detected metastases in only 4 per cent of patients overall (1 per cent–one of 89–for $T_{1/2}$ tumours). It detected only 50 per cent of proven metastases, had no higher yield than other investigations and did not positively affect management in these patients. There were 16 unrelated findings, mainly in the head and pelvis, where no metastases were found. These included two meningiomas (patients under observation) and four ovarian masses (three benign cysts at laparotomy and one presumed cyst, unchanged on follow-up CT).

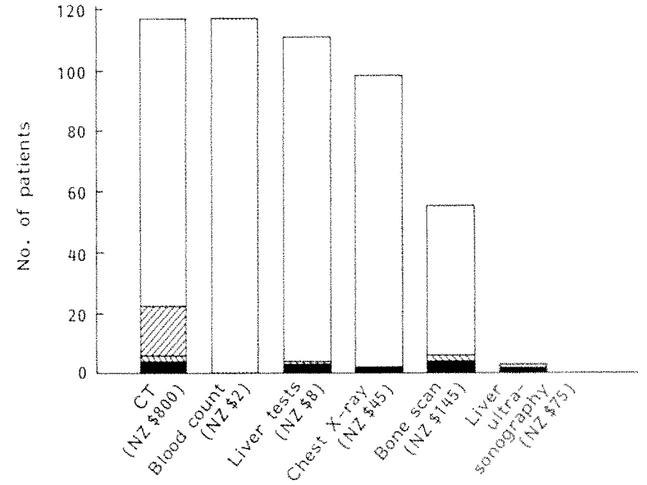

Figure 1 *Frequency of true metastases, false-positive and unrelated findings identified by the various investigations. The cost for each test is shown. CT, computed tomography.* ■, *Metastases correctly identified;* ▧, *false-positive scans;* ▨, *unrelated findings;* ⬚, *normal findings*

Two patients had false-positive scans, leading to unnecessary laparotomy in one and delay of definitive locoregional treatment in the other. CT failed to identify metastases detected by other investigations in four patients: three on bone scintigraphy (only one outside the CT field) and one with hepatic secondaries detected by abnormal biochemistry and positive liver ultrasonography.

Of those receiving definitive local treatment and with a normal scan there have been 18 relapses, eight within 1 year of CT. Early relapse was not related to T stage or nodal status.

Discussion

CT is much more expensive, but has no higher yield, than basic investigations in detecting metastases in asymptomatic patients with primary breast cancer. Unrelated findings may lead to considerable anxiety and to unnecessary operations. False-positive findings similarly complicate management, and a negative CT scan does not preclude early relapse.

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Pathophysiology, recognition and management of pneumoretroperitoneum

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The medical records of 15 patients found to have pneumoretroperitoneum in a 10-year period were reviewed. The cause of retroperitoneal emphysema was infection in six patients, trauma in five and iatrogenic in four. Emphysema was confined to the retroperitoneum in 11 patients, and extended to the mediastinum in four and to the soft tissue of the neck in three. Failure to diagnose pneumoretroperitoneum resulted in delayed intervention in two patients. One patient with pneumoretroperitoneum and pneumoperitoneum secondary to a lung lesion underwent unnecessary laparotomy. Outcome was favourable in these three patients. The presence of air in the retroperitoneum is not dangerous but its early recognition and detection of the source are important as septic conditions may be involved.

The retroperitoneum communicates with the mediastinum and neck, and has extensions into the mesentery and abdominal wall (the preperitoneal space)[1]. Aberrant air in this space arises mainly from gastrointestinal or respiratory tract rupture and from gas-forming infections, and may diffuse to any one of these areas. Infiltration of air into the retroperitoneum has discrete diagnostic features. Its recognition is important since rupture of a segment of the gastrointestinal tract is frequently involved. Failure to identify this condition delays diagnosis and may result in significant sepsis. Awareness of the possible aetiology and anatomical routes in the retroperitoneum should help select appropriate diagnostic and surgical interventions.

Patients and methods

The medical records of 15 patients presenting with pneumoretroperitoneum between 1981 and 1990 were reviewed retrospectively. There were eight men and seven women of median age 64 (range 18–81) years. During the study period, 18 868 abdominal operations (14 766 elective, 4102 emergency) were performed in the same department. One of 3746 inguinal hernia repairs was complicated by colonic perforation leading to pneumoretroperitoneum. Four of 565 patients with colonic diverticulitis developed extensive pneumoretroperitoneum following perforation. Of 20 659 gastroscopies and 9210 colonoscopies performed, there was one instance of pneumoretroperitoneum after gastroscopy without biopsy and two after colonoscopy with biopsy. During the last 3 years of the study period additional procedures such as biopsy or polypectomy were performed in 55 per cent of all colonoscopies (1592 of 2905 procedures). No case of pneumoretroperitoneum was noted after approximately 250 endoscopic sphincterotomies, 162 of which were performed during the last 3 years of the study.

Results

Presentation

The causes of pneumoretroperitoneum are summarized in *Table 1*. Emphysema was confined to the retroperitoneum in 11 patients, and extended to the mediastinum in four and to the soft tissue of the neck in three. In one patient with a diverticular perforation at the rectosigmoid junction, air was not seen on plain abdominal radiography but was detected in the mediastinum and neck on chest radiography. The abnormal infiltration of air was detected without delay in 12 patients and its recognition prompted further radiological studies to identify the underlying disease and/or immediate surgical intervention. In three patients radiographic features were missed or falsely interpreted, resulting in delayed or inappropriate management.

Treatment

Pneumoretroperitoneum was managed medically by fasting, hydration and intravenous antibiotics in four patients: three had a gastrointestinal perforation following endoscopy (one duodenal, two rectal) and one had a duodenal stump leak. Conservative treatment seemed appropriate in patients with endoscopic perforation of the colorectum provided there were no signs of active infection since the bowel had been prepared and had no underlying stenotic lesion (*Figure 1*). Fatal sepsis developed in two patients who were denied surgical intervention because of their poor state of health and grave prognosis: one patient with a rectal perforation following biopsy had Child's grade C alcoholic cirrhosis and the other had undergone a palliative Billroth II gastrectomy 10 weeks previously for antral adenocarcinoma (T_4N_3).

Surgical management included procedures to treat the cause of the pneumoretroperitoneum and to drain a focus of infection when present. Hartmann's procedure was performed in four patients with perforated diverticulitis and in one with an iatrogenic lesion of the sigmoid colon following inguinal hernia repair. Colostomy, rectal wash-out, debridement and perirectal drainage were performed in three patients with an extensive perineal wound. Laparotomy ruled out associated abdominal lesions and confirmed the pneumoretroperitoneum. Removal of the prosthesis, local drainage and systemic antibiotic therapy were successful in a patient with an infected hip prosthesis that had produced sufficient gas to extend along the psoas muscle (*Figure 2*).

Delayed or erroneous diagnosis

Three patients had a delayed or false diagnosis.

Table 1 *Cause of pneumoretroperitoneum in 15 patients*

Infectious	
Perforated sigmoid diverticulitis	4
Duodenal stump leak	1
Hip-joint anaerobic abscess	1
Traumatic	
Extensive perineal wound	3
Duodenal tear	1
Lung contusion	1
Iatrogenic	
Colonoscopy with biopsy	2
Gastroscopy after Billroth II gastrectomy	1
Colonic injury after inguinal herniorrhaphy	1

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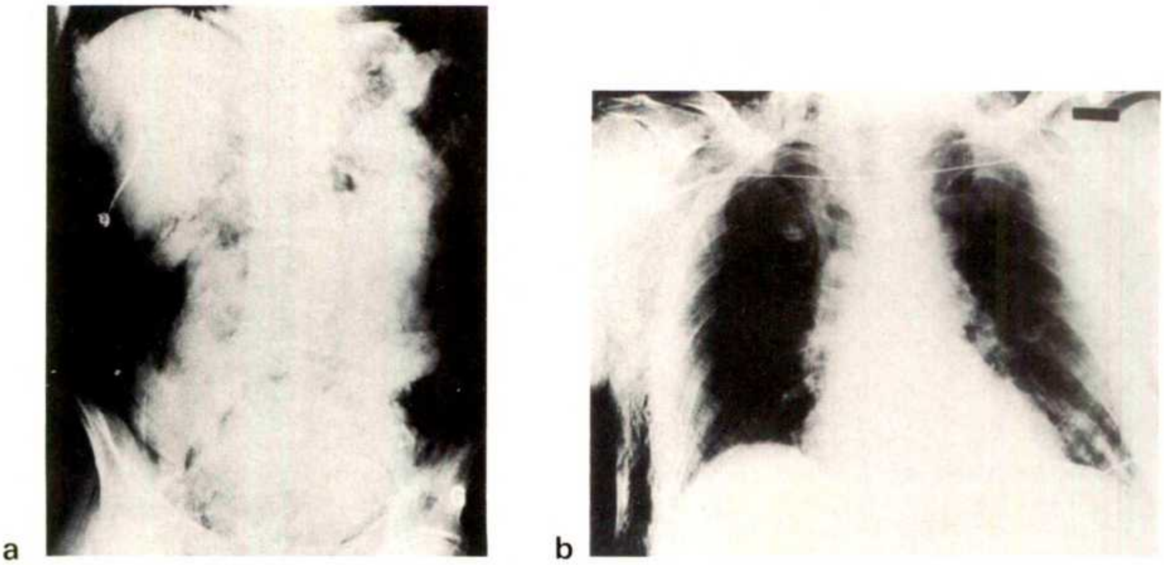

Figure 1 *Extensive emphysema following colonoscopy with biopsy of the rectosigmoid junction in a 75-year-old man.* **a** *Abdominal radiography shows pneumoretroperitoneum with some of the pelvic structures and the psoas muscle 'dissected' by air infiltration.* **b** *Pneumomediastinum and emphysema in the neck and the thoracic wall are visible on the chest radiograph*

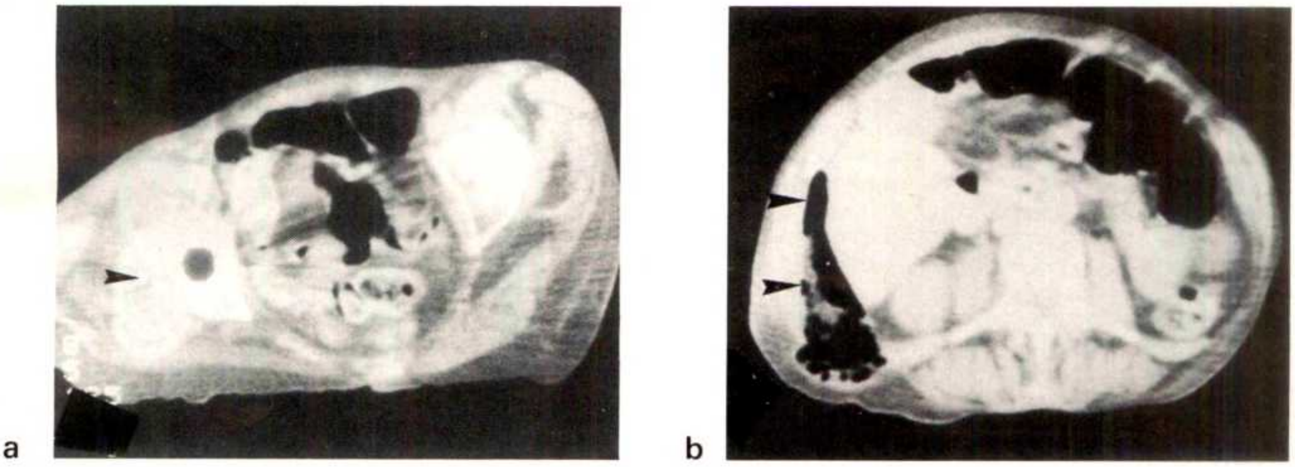

Figure 2 *Computed tomograms of the* **a** *pelvis and* **b** *abdomen of a 67-year-old woman with a prosthetic hip infection. In the pelvic image an abscess (arrow) surrounds the prosthesis. The abdominal image shows air infiltration in the retroperitoneum and in the preperitoneal space (arrows) of the abdominal wall between the transversalis fascia and the parietal peritoneum*

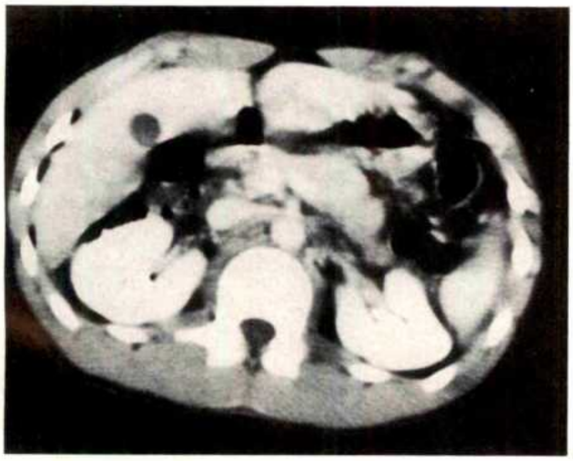

Figure 3 *Computed tomogram of a 19-year-old man (patient 1) with blunt abdominal trauma and perforation of the second part of the duodenum. Air infiltrated the retroperitoneum, as can be seen around the kidneys. This was missed initially and resulted in delayed treatment of the duodenal tear*

Patient 1. A 19-year-old man was involved in a motorcycle accident. Pneumoretroperitoneum adjacent to the duodenum, although visible on computed tomography, was missed initially (*Figure 3*). Some 2 days later the patient became feverish with signs of ileus and a repeat scan showed a retroperitoneal collection close to a duodenal perforation. At operation, a tear in the second part of the duodenum was confirmed. Despite surrounding retroperitonitis the duodenal perforation was closed primarily and the area widely drained. A fistula through the drain track resolved spontaneously in 3 weeks.

Patient 2. An 81-year-old woman was transferred with sequential organ failure. Abdominal palpation, and rectal and pelvic examination revealed a tender mass in the left lower quadrant. Chest radiography showed pneumomediastinum and emphysema of the neck. The latter had been noticed 2 days earlier and attributed to the placement of a central line. Air in the retroperitoneum was not apparent on abdominal radiography. Laparotomy showed perforated sigmoid diverticulitis in the retroperitoneum and extensive pneumoretroperitoneum. Hartmann's procedure was performed and the retroperitoneum drained. The patient recovered rapidly; renal and respiratory function returned to normal.

Patient 3. A 31-year-old man was intubated at the scene of a car accident because of coma. The patient was ventilated manually during transportation. Chest radiography revealed pneumomediastinum and emphysema of the soft tissue of the neck. Computed tomography showed pneumoretroperitoneum and pneumoperitoneum. No lesions were seen in the chest or abdomen. Laryngoscopy, bronchoscopy and contrast studies excluded a tracheobronchial or oesophageal lesion. Exploratory laparotomy was undertaken but proved normal. The patient recovered uneventfully.

Discussion

The retroperitoneum is divided by fasciae that provide preferential ways through which gas or fluid may spread. The retroperitoneum communicates with the mediastinum (through the diaphragmatic hiatus) and with the femoral vessels and spermatic cord inferiorly, and is continuous with the mesenteric and preperitoneal interstitium. The mediastinum communicates with the bronchovascular interstitium (via the pulmonary hilar structures) and with the visceral space of the neck[1]. A continuum therefore exists connecting the visceral space of the neck, the mediastinum, the retroperitoneum, the mesenteric and testicular interstitia and the root of the lower extremities.

Emphysema of the retroperitoneum, mediastinum and visceral space of the neck may arise from three pathological situations: disruption of cutaneous or gastrointestinal mucosal barriers, infection with gas-forming organisms, and rupture of the respiratory tract or alveoli. The progression of gas in tissues is determined mainly by pressure gradients, tissue resistance and quantity of gas. The retroperitoneum and mediastinum are for the most part covered by an air-tight layer of mesothelial tissue. This layer may break under excessive pressure and result in pneumothorax and/or pneumoperitoneum. When the air leak is distant from the retroperitoneum, large quantities of air and a high pressure gradient are necessary for the emphysema to reach the retroperitoneum. Examples include blunt chest trauma with rupture of a major airway[2], mechanical ventilation and Boerhaave's syndrome[3].

Rupture of a retroperitoneal structure may occur spontaneously, as in perforated duodenal ulcer, ulcerative colitis[4] or colonic diverticulitis, and is usually confined to the abdomen because of a low pressure gradient. Pneumoretroperitoneum following endoscopic procedures is extensive, however, because of the high pressure gradient generated and the large volume of air insufflated; it is thus sometimes associated with pneumoperitoneum and pneumothorax[5].

The four largest emphysemas in the present series occurred after colonoscopy with biopsy (*Figure 1*), following vigorous manual ventilation, after a sigmoid perforation was left untreated for 10 days, and after a hip infection (*Figure 2*). In the last case the extent of dissection probably resulted from gas pressure within the abscess and the lytic action of bacterial enzymes. Pneumoretroperitoneum complicated gastroscopy in two reported cases[6,7] and in one patient in the present series. All three patients had undergone partial gastrectomy a few weeks previously and air probably travelled through adhesions at the anastomotic site into the retroperitoneum. Of note in the present series is the absence of pneumoretroperitoneum after endoscopic sphincterotomy. Small amounts of air may have infiltrated the retroperitoneum in some patients, remaining clinically quiescent and escaping detection by cholangiography.

Pneumoperitoneum may occasionally have a pulmonary origin when a major air leak and high pressure gradient have been produced. A peritoneal tap for pressure release is sometimes required in newborn babies with membrane hyaline disease who are ventilated with high pressures because of stiff premature lungs[8,9]. One of the present patients with blunt chest trauma developed extensive emphysema with pneumoperitoneum after vigorous mechanical ventilation. Evron *et al.*[2] reported a similar patient with pneumoperitoneum following a tension pneumothorax. Observation was carried out and saved the patient an unnecessary exploration.

Interstitia of the retroperitoneum, mediastinum and visceral space of the neck are 'crossroads' where gas and fluid of different origins may accumulate. Continuous fascial planes connect these areas, permitting aberrant air arising in any one of them to spread elsewhere. While such air is not in itself dangerous, prompt recognition of its origin is essential since serious septic conditions may be involved.

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Anterior *versus* posterior reconstruction after transhiatal oesophagectomy: a randomized controlled trial

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In a prospective randomized trial the clinical results after transhiatal oesophagectomy with reconstruction in the anterior mediastinum (51 patients) or posterior mediastinum (45 patients) were compared. There were no differences in age, preoperative risk factors, tumour stage and local (surgical) complications between the two groups. However, reconstruction in the posterior mediastinum was associated with significantly fewer days spent in the intensive therapy unit (9 versus *14), fewer cardiopulmonary complications (13* versus *25 per cent) and lower mortality (30-day mortality rate 2* versus *6 per cent; hospital mortality rate 4* versus *10 per cent). These data show superiority of reconstruction in the posterior mediastinum after transhiatal oesophagectomy. This route is strongly recommended, particularly for patients with cardiopulmonary risk factors.*

Transhiatal oesophagectomy has become a valid alternative to the transthoracic approach for oesophageal resection[1–5]. Most authors agree that the indications for transhiatal oesophagectomy are adenocarcinoma of the distal oesophagus, early squamous cell carcinoma of the distal oesophagus ($T_{1/2}$ tumours) and benign conditions of the oesophagus that require resection such as caustic injuries[6–9].

After transhiatal resection the surgeon has the choice between reconstruction in the anterior or posterior mediastinum, provided complete macroscopic and microscopic tumour excision (R_0 resection) has been achieved. Reconstruction in the anterior mediastinum may be considered superior because it allows postoperative irradiation of the oesophageal bed. Recently, however, improvements in patient selection and resection techniques have decreased the rate of local tumour recurrence to below 10 per cent[10]. Furthermore, tumour recurrence was rarely found to cause obstruction of the interposed organ.

To investigate whether reconstruction in the anterior mediastinum offers any advantages over that in the posterior mediastinum, a randomized controlled trial was performed.

Patients and methods

This study was performed between 1 October 1986 and 31 December 1988. All patients with oesophageal carcinoma who underwent transhiatal oesophagectomy and reconstruction by gastric interposition were included (*Table 1*). Patients who received preoperative radiotherapy or chemotherapy and those with previous gastric resection who required colonic interposition were excluded.

A total of 96 patients met the inclusion criteria. In 79 transhiatal oesophagectomy was performed for adenocarcinoma of the distal oesophagus; 17 had early squamous cell carcinoma ($T_{1/2}$) of the distal oesophagus. Cervical oesophagogastrostomy was performed in all cases; this allowed the choice between reconstruction in the anterior or posterior mediastinum. After obtaining informed consent the route of reconstruction (anterior or posterior mediastinum) was chosen in a random fashion before operation.

Age, tumour type and stage, and preoperative risk factors are shown in *Tables 2* and *3*. There were no significant differences between patients who had anterior or posterior reconstruction. All patients underwent R_0 resection, i.e. complete macroscopic and microscopic tumour removal.

Transhiatal oesophagectomy was performed in a standardized fashion as described previously[5,9,11]. After blunt dissection the gastric tube created parallel to the major curvature was interposed either

Table 1 *Details of 160 patients undergoing transhiatal oesophagectomy*

Reconstruction	
Gastric interposition	140
Colonic interposition	20
Preoperative radiotherapy or chemotherapy	40
$R_{1/2}$, incomplete microscopic or macroscopic tumour resection	6

Table 2 *Age, and tumour type and stage of 96 randomized patients undergoing transhiatal oesophagectomy with gastric interposition*

	Anterior mediastinum	Posterior mediastinum	Total
No. of patients	51	45	96
Mean age (years)	61·5	59·2	60·8
Adenocarcinoma	43	36	79
Squamous cell carcinoma	8	9	17
UICC stage			
I	7	8	15
IIA	9	10	19
IIB	10	11	21
III	25	16	41

UICC, Union Internacional Contra la Cancrum

Table 3 *Preoperative risk factors*

	Anterior mediastinum (*n* = 51)	Posterior mediastinum (*n* = 45)	Total (*n* = 96)
Risk			
Respiratory	14 (27)	12 (27)	26 (27)
Cardiac	6 (12)	4 (9)	10 (10)
Hepatic	6 (12)	5 (11)	11 (11)
ASA grade			
I or II	28 (55)	24 (53)	52 (54)
III or V	23 (45)	21 (47)	44 (46)

Values in parentheses are percentages. ASA, American Society of Anesthesiologists

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retrosternally (anterior mediastinum) or in the oesophageal bed (posterior mediastinum). Postoperative management was similar for both groups and included positive-pressure ventilation for 48 h after the procedure[12].

All intraoperative and postoperative data (duration of anaesthesia, blood loss, cardiopulmonary function, days in the intensive therapy unit, etc.), postoperative complications (surgical and other) and mortality were documented prospectively and evaluated at the end of the study. Details of the assessment of cardiopulmonary function are described elsewhere[13]. Student's t test, the Wilcoxon signed rank test and χ^2 analysis were used for statistical evaluation. $P < 0.05$ was considered significant.

Results

According to the preoperative randomization, 51 patients underwent reconstruction in the posterior and 45 reconstruction in the anterior mediastinum. The duration of anaesthesia and volume of intraoperative blood loss were similar in the two groups (*Table 4*).

In both groups the intrapulmonary right–left shunt (Q_S:Q_T) was markedly increased during the immediate postoperative period compared with preoperative values (*Figure 1*). The peak in shunt volume was seen 12 h after the procedure. Compared with that after reconstruction in the anterior mediastinum, respiratory function was less compromised in patients who underwent posterior reconstruction. This difference was significant 24 h after operation.

In addition, the cardiac index was significantly decreased throughout the first 36 h after operation in patients with reconstruction in the anterior mediastinum (*Figure 2*). This decrease in cardiac index was due primarily to a reduction in stroke volume index, which was compromised throughout the postoperative monitoring period in these patients (*Figure 3*).

Table 4 *Intraoperative and postoperative data*

	Anterior mediastinum (n = 51)	Posterior mediastinum (n = 45)	P
Duration of anaesthesia (h)	5	5	n.s.
Blood loss (units)	3	2	n.s.
Duration of postoperative ventilation (h)	49	50	n.s.
Stay in intensive therapy unit (days)	14	9	<0·05
Hospital stay (days)	24	23	n.s.

Values are means. n.s., Not significant

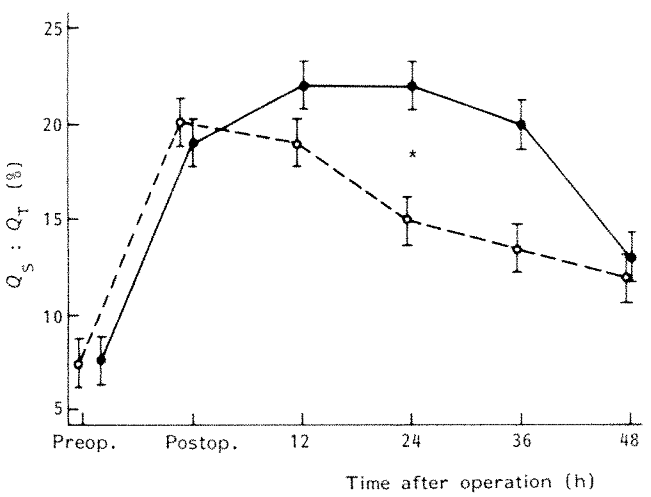

Figure 1 *Mean(s.d.) intrapulmonary right–left shunt* (Q_S:Q_T) *after transhiatal oesophagectomy.* ——, *Gastric interposition in the anterior mediastinum* (n = *51*); – – –, *gastric interposition in the posterior mediastinum* (n = *45*). *P < *0·05* (*Student's* t *test*)

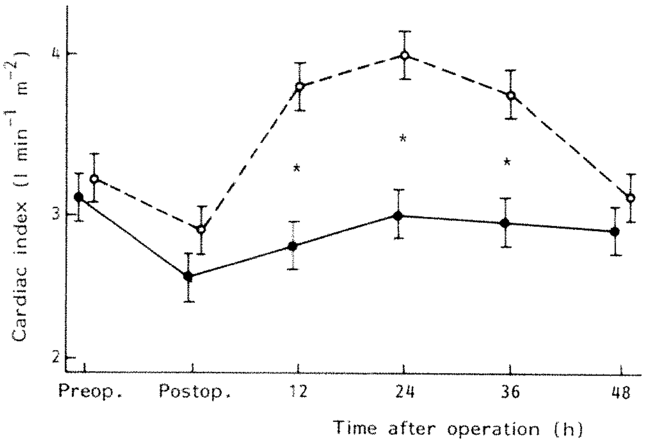

Figure 2 *Mean(s.d.) cardiac index after transhiatal oesophagectomy.* ——, *Gastric interposition in the anterior mediastinum* (n = *51*); – – –, *gastric interposition in the posterior mediastinum* (n = *45*). *P < *0·05* (*Student's* t *test*)

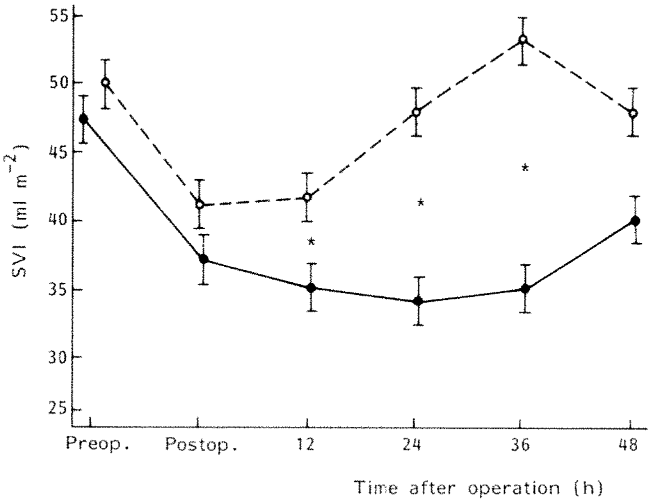

Figure 3 *Mean(s.d.) stroke volume index (SVI) after transhiatal oesophagectomy.* ——, *Gastric interposition in the anterior mediastinum* (n = *51*); – – –, *gastric interposition in the posterior mediastinum* (n = *45*). *P < *0·05* (*Student's* t *test*)

Table 5 *Complications and mortality*

	Anterior mediastinum (n = 51)	Posterior mediastinum (n = 45)	Total (n = 96)
Surgical complications			
Anastomotic leakage	5 (10)	5 (11)	10 (10)
Sepsis	2 (4)	2 (4)	4 (4)
Other	4 (8)	3 (7)	7 (7)
Total	11 (22)	10 (22)	21 (22)
General complications			
Respiratory	7 (14)	4 (9)	11 (11)
Cardiac	5 (10)	1 (2)	6 (6)
Hepatic	1 (2)	1 (2)	2 (2)
Total	13 (25)	6 (13)	19 (20)
Mortality rate			
Hospital	5 (10)	2 (4)	7 (7)
30-day	3 (6)	1 (2)	4 (4)

Values in parentheses are percentages

The clinical data are shown in *Tables 4* and 5. Compared with anterior reconstruction, the posterior mediastinum procedure was associated with fewer days in the intensive therapy unit (9 *versus* 14), decreased frequency of general complications (13 *versus* 25 per cent) and lower mortality

(30-day mortality rate 2 *versus* 6 per cent; hospital mortality rate 4 *versus* 10 per cent).

Discussion

A lower complication rate has been claimed repeatedly for transhiatal oesophagectomy compared with the transthoracic approach[2-4]. To date, however, a decreased risk for transhiatal oesophagectomy could not be confirmed in clinical trials[14-16]. Rather, the decrease in postoperative mortality rate following oesophageal resection in recent years appears to be due to improved patient selection, standardization of resection technique and advances in perioperative and postoperative care[17,18]. These factors have a similar influence on transthoracic and transhiatal procedures[19].

According to the principles of oncological surgery, reconstruction in the oesophageal bed, i.e. the posterior mediastinum, should be attempted only after R_0 resection. In patients with advanced disease or when complete tumour resection is questionable, reconstruction should be performed in the anterior mediastinum to avoid obstruction of the interposed organ by local tumour recurrence and to allow postoperative irradiation of the oesophageal bed[9,18]. Because of patient selection and the high rate of R_0 resection, local tumour recurrence was not likely in the present population[10]. A random preoperative allocation of the route of reconstruction could therefore be justified for the present study.

Re-establishment of gastrointestinal continuity by a gastric tube in the mediastinum results in mechanical compression of the adjacent lung[20,21]. In the present study this was reflected by an increase in the intrapulmonary right–left shunt (Q_S:Q_T) during the early postoperative period. In an experimental study Niederle *et al.*[6] have shown a significant increase in intrapulmonary shunting in animals who underwent reconstruction in the posterior mediastinum compared with those undergoing anterior reconstruction. There were no significant differences in respiratory function between the two routes of reconstruction in the present study (*Figure 1*). The prophylactic 48-h postoperative positive-pressure ventilation that was performed in all the present patients to reduce compression atelectasis may explain this observation[12,13,21].

In contrast to the lack of difference in respiratory function between the two routes of reconstruction, the present study showed differences in haemodynamic function. The cardiac index, the most important cardiac parameter, dropped markedly immediately after the surgical procedure. This drop was similar in both groups of patients and was probably secondary to hypoxia and the negative inotropic effect of anaesthesia[20,21]. There was, however, a marked delay in normalization of the cardiac index during the first days after anterior reconstruction (*Figure 2*). Obstruction of the right ventricle by the interposed gastric tube or paradoxical movements of the septum and the resulting compromise in stroke volume index may explain this observation[6].

The compromised cardiac and respiratory function during the postoperative period is reflected in the clinical results. Cardiorespiratory complications, intensive therapy unit stay and mortality rate were greater after reconstruction in the anterior mediastinum. Similar results have been reported by Nishi *et al.*[22] in a retrospective analysis. In that study reconstruction in the posterior mediastinum following transthoracic oesophagectomy resulted in a 50 per cent decrease of respiratory complications compared with anterior reconstruction.

In the present study the route of reconstruction did not influence the rate of surgical complications. The frequency of cervical anastomotic leaks was similar in both patient groups (*Table 5*). In most patients the leak closed spontaneously after drainage.

The present study shows no differences in levels of blood loss, duration of postoperative ventilation, and surgical complications between the two methods of reconstruction (*Tables 4* and *5*). Reconstruction in the posterior mediastinum, however, had some major advantages, including a lower rate of cardiorespiratory complications, a shorter stay in the intensive therapy unit and decreased hospital mortality rate. In addition, posterior reconstruction offers several other advantages. The procedure is easier and can be performed more quickly because the diameter of the thoracic inlet is wider posteriorly than anteriorly and the surgeon does not have to create a second tunnel. Also, the interposed organ protects the tracheobronchial tree by tamponading the posterior mediastinum. This may become important if the tracheobronchial system is injured during the procedure. Finally, in the authors' experience postoperative swallowing is better after posterior reconstruction and dilatation easier to perform. An exact analysis of these factors, however, requires further study.

In summary, the present study documents the superiority of reconstruction in the posterior mediastinum following transhiatal oesophagectomy compared with reconstruction in the anterior mediastinum. Provided R_0 resection has been performed, posterior reconstruction should be the procedure of choice, particularly in patients at increased cardiorespiratory risk.

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Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

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Venous thromboprophylaxis in oesophageal cancer surgery

In a retrospective study of 127 patients who underwent resection for oesophageal cancer without anticoagulant thromboprophylaxis, the incidence of clinically established postoperative deep vein thrombosis (DVT) was 1·6 per cent. In a prospective study the Sue-Ling DVT risk factor index was calculated for 53 consecutive patients with oesophageal cancer; the mean(s.d.) value was $-4\cdot4(3\cdot5)$. For 29 patients who underwent resection the following policy of thromboprophylaxis was applied. Patients undergoing transthoracic oesophagectomy with risk score > -4 (four patients) and those undergoing transhiatal resection with risk score > -1 (four) received both anticoagulant and mechanical thromboprophylaxis; the remaining 21 patients received only mechanical thromboprophylaxis. No patient developed DVT after operation. There were no haemorrhagic complications in the group undergoing anticoagulant thromboprophylaxis. The selective approach, based on the Sue-Ling risk factor index and type of operation, spared 72 per cent of the patients operated on from undergoing anticoagulant thromboprophylaxis and produced favourable results in this small series.

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Oesophagectomy with reconstruction is a long and extensive procedure that is followed by a relatively lengthy period of bed-rest. The majority of patients are smokers and over 50 years old. All these factors increase the incidence of deep vein thrombosis (DVT)[1–4], and patients undergoing surgery for oesophageal cancer require thromboprophylaxis. Despite this, we believe that venous thromboembolic disease is not a common complication of oesophageal cancer surgery and that general anticoagulant thromboprophylaxis may not be required. The aims of this study were to estimate the risk of DVT in patients with oesophageal carcinoma and to evaluate the incidence of DVT and pulmonary embolism after oesophageal cancer surgery using a selective anticoagulant thromboprophylaxis regimen.

Patients and methods

The first part of the study was retrospective and based on 127 patients with oesophageal cancer (91 men, 36 women; mean(s.d.) age 58·7(7·9) years) who underwent oesophagectomy with cervical oesophagogastrostomy without anticoagulant thromboprophylaxis between 1979 and 1991. Clinical records and pathology reports were reviewed in detail and data regarding postoperative DVT and embolism recorded. Five patients received mechanical thromboprophylaxis with graduated compression stockings and all patients underwent early exercise and ambulation. The diagnosis of DVT and embolism was based on clinical grounds and/or findings at autopsy.

The second part of the study was prospective and based on 53 consecutive patients with oesophageal cancer (36 men, 17 women; mean(s.d.) age 60·9(8·2) years) treated during 1991. A DVT risk factor index (I) was calculated using the formula of Sue-Ling *et al.*[5]:

$$I = -8\cdot08 + 0\cdot185a + 0\cdot008b - 2\cdot24c + 2\cdot02d - 0\cdot054e - 0\cdot118f - 0\cdot006g$$

where a is age in years, b is euglobulin lysis time in minutes, c is previous abdominal surgery (yes, 1; no, 0), d is presence of varicose veins (present, 1; absent, 0), e is amount of antithrombin III as a percentage, f is number of cigarettes smoked per day, and g is platelet count ($\times 10^6$ per millilitre). A shortened predictive index was calculated as follows:

$$I_S = -11\cdot5 + 0\cdot133a + 0\cdot006b$$

Laboratory methods were the same as those used by Sue-Ling *et al.*[5] and Blix[6] except for the concentration of antithrombin III, which was measured using an enzyme-linked immunosorbent assay photometer (Behring, Frankfurt, Germany).

Of the 53 patients, 29 underwent potentially curative resection. Ten who had tumours of the middle third of the oesophagus and were in good general condition underwent oesophagectomy through a right thoracotomy. The remaining 19 underwent oesophagectomy by blunt dissection. All 29 patients underwent reconstruction with the stomach anastomosed to the cervical oesophagus, and all received mechanical thromboprophylaxis.

Sue-Ling *et al.*[5] reported that patients with large positive scores are most likely to have postoperative DVT, that 91 per cent of patients with DVT are correctly identified if a cut-off value of -1 is used, and that no DVT occurs among those with risk score < -4. The policy in the present study of selective anticoagulant thromboprophylaxis was based on these observations and the perceived risk of haemorrhagic complications. The thoracic approach provides good control of haemostasis, and for patients undergoing transthoracic oesophagectomy a cut-off value of -4 was used; four of the ten patients had a risk score > -4 and received anticoagulant thromboprophylaxis. Control of haemostasis can be problematic in blunt oesophageal resection and it was felt that anticoagulant thromboprophylaxis might increase the frequency of haemorrhagic complications; for the 19 patients undergoing blunt oesophagectomy a cut-off value of -1 was used. Four of these patients had a risk score > -1 and received anticoagulant thromboprophylaxis; the remaining 15 did not.

Anticoagulant thromboprophylaxis consisted of low-dose heparin (5000 units) given subcutaneously 2 h before surgery and then at intervals of 12 h. Mechanical thromboprophylaxis included graduated compression stockings, and early exercise and ambulation.

All patients underwent clinical surveillance and real-time duplex B-mode ultrasonography (Toshiba SSA-100A; Toshiba, Tokyo, Japan) using a 3·5-MHz and 7-MHz probe for DVT, both before and after operation. Ultrasonography was performed in 11 patients twice after operation: the first time on days 4–5 after surgery and the second time on days 9–12. In the remaining 18 patients ultrasonography was performed only once, 8–12 days after operation. All duplex scans were performed by the same experienced operator (Z. M.).

Results

Among the patients analysed retrospectively who were operated on without anticoagulant thromboprophylaxis, the incidence of clinically manifested DVT and/or embolism was two of 127 (1·6 per cent). One patient died from pulmonary thromboembolism; diagnosis was based on clinical symptoms and confirmed by autopsy, which identified a clinically silent DVT of the leg as the source of emboli. Clinically symptomatic DVT

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of the calf occurred in a further patient who was successfully treated conservatively.

The mean(s.d.) euglobin lysis time for the 53 patients with oesophageal cancer was 198(73) min, and the mean(s.d.) DVT risk factor index was $-4{\cdot}4(3{\cdot}5)$. Four patients (8 per cent) had a positive index, 45 (85 per cent) had an index < -1, and 30 (57 per cent) had an index < -4; the 95 per cent confidence interval for the DVT risk factor index values obtained was $-10{\cdot}20$ to $1{\cdot}05$. The mean(s.d.) value of the shortened predictive index was also low, $-2{\cdot}7(1{\cdot}0)$. It has been shown[5] that at a cut-off value of $-1{\cdot}5$ this index has a sensitivity of 93 per cent and a specificity of 83 per cent. Of the 53 patients, only two had a shortened predictive index $> -1{\cdot}5$. All patients who underwent resection had a shortened index $< -1{\cdot}5$.

None of the 29 patients undergoing resection developed clinically or ultrasonographically detectable DVT after operation. There were no haemorrhagic complications in the group receiving anticoagulant thromboprophylaxis.

Discussion

It has been suggested that routine anticoagulant thromboprophylaxis in major general abdominal surgery minimizes the incidence of thromboembolic complications and is cost-effective, whereas selective treatment is unsatisfactory and expensive[7,8]. However, anticoagulant thromboprophylaxis may also increase the frequency of haemorrhagic complications[9,10]. Although there are no published data on this issue, it might be anticipated that routine anticoagulant thromboprophylaxis may even be dangerous for patients who undergo blunt oesophageal resection. Control of haemostasis is generally delicate in these patients and the average intraoperative blood loss[11], even without thromboprophylaxis, is about 1000 ml.

Larger series describing results of oesophageal cancer resection have shown that the incidence of postoperative thromboembolic complications rarely exceeds 1 per cent[11,12]. A similar incidence was recorded in the present patients studied retrospectively, who received no anticoagulant thromboprophylaxis. Although it should be emphasized that the real incidence of DVT is much higher than can be appreciated from a retrospective study, the vast majority of the present patients with oesophageal cancer were found to have a low DVT risk factor index and shortened predictive index. It seems unlikely that patients with oesophageal cancer are at particularly high risk for postoperative DVT.

Mechanical thromboprophylaxis has recently been shown in general surgical patients to be as effective as anticoagulant therapy[13]. Hence, weighing the risk of developing thrombosis against the benefits, cost and potential complications of general anticoagulant thromboprophylaxis, a selective approach to anticoagulation in oesophageal cancer surgery seems justified if it proves possible to identify correctly the small subset of patients who are likely to develop DVT. A similar effect would be achieved by identification of those who are unlikely to develop DVT; they could safely be spared anticoagulant thromboprophylaxis.

In the present series, the mean(s.d.) age, euglobin lysis time, DVT risk factor index and shortened predictive index were similar to the values obtained by Sue-Ling *et al.*[5], which suggests that the results should be comparable. Hence, the selective approach based on the Sue-Ling risk factor index and type of operation seemed safe and reasonable. Such a regimen spared 21 of the 29 patients undergoing operation from anticoagulant thromboprophylaxis and produced favourable results in this small series. However, duplex scanning may have missed some small distal thrombi. Although the total incidence of DVT in the present series may have been underestimated, such thrombi are probably not of great clinical significance.

The present preliminary findings suggest that there is a potential case for selective anticoagulant thromboprophylaxis in patients undergoing surgery for oesophageal cancer. The risk factor index can be calculated rapidly, which is especially useful to surgeons with a heavy clinical load. Larger controlled studies are necessary to define more accurately the best thromboprophylactic regimen for the patient with oesophageal cancer who undergoes surgery.

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Penetrating external injuries of the oesophagus and pharynx

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Fifty-one instances of oesophageal perforation were discovered when the records of 18 588 patients with external penetrating injuries of the neck, chest and abdomen were reviewed. Of these, 33 resulted from stab wounds, 17 from bullets and one from hyperextension of the neck. There were 15 perforations of the pharynx and 36 of the oesophagus. Oesophagography in a lateral decubitus position demonstrated the perforation in all 16 patients in whom it was used. In 45 patients simple repair within 24 h of injury was performed (mortality rate 11 per cent). In six patients with a delay of more than 24 h in the repair of the thoracic oesophagus, special techniques were preferred. In two patients an oesophageal diversion–exclusion method was used; one such patient died. In four patients repair over a large-bore T tube was carried out with one death. The main cause of mortality was associated spinal injury (four deaths).

A large number of patients with penetrating injuries of the neck, chest and abdomen are treated at Baragwanath Hospital. The oesophagus is rarely injured because of its central and relatively protected position. Early investigation and repair of potential oesophageal injuries is of importance: several studies have shown substantially higher mortality rates following repair delayed more than 24 h from the time of injury[1,2].

Patients and methods

The records of all patients with trauma to the neck, chest or abdomen presenting between January 1988 and December 1991 were reviewed retrospectively for oesophageal injuries. All external injuries were examined but internal trauma such as iatrogenic perforation was excluded. The neck was surgically explored only when certain criteria were met[3]. The indications for thoracotomy in the case of chest or neck injury have been described elsewhere[4]. Oesophagography or oesophagoscopy was carried out if: (1) a penetrating injury of the neck or chest was anatomically directed towards the oesophagus; and (2) there were no indications for immediate surgical exploration. The need for oesophagography or oesophagoscopy was considered more compelling when clinical findings (surgical emphysema, dysphagia, haematemesis) or radiological results (surgical emphysema, haemopneumothorax, widening of the mediastinum, increased distance from trachea to vertebral column) were suspicious of, or compatible with, oesophageal perforation. Water-soluble contrast media were preferred since Gastrografin (Berlimed, Johannesburg, South Africa) can produce severe irritation in the airway and lungs.

Injuries of the abdominal oesophagus were discovered at laparotomy undertaken in patients with an acute abdomen.

A nasogastric tube was usually introduced and the neck explored through an incision along the anterior border of the sternomastoid. When less than 24 h had elapsed between injury and surgery, primary repair of the oesophagus was performed, usually with a single layer of interrupted non-absorbable sutures. After more than 24 h oesophageal diversion and exclusion as described by Johnson *et al.*[5] was added. Jejunostomy rather than gastrostomy was used. In one patient the proximal stump of the divided cervical oesophagus would not reach the skin and a tube oesophagostomy was constructed.

T tube splinting was recently introduced for late repair. A large 22–24-Fr tube was inserted via the perforation and the ends of its limbs cut to project 2·5 cm above and below the lesion[6]. The long limb was brought out through the chest wall. The perforation was closed above and below the tube with single all-layer interrupted sutures. This method has already been used in earlier years to treat 'spontaneous' rupture of the oesophagus[7].

Results

Review of the records of 440 patients with neck, 8688 with thoracic and 9460 with abdominal penetrating injuries produced 51 subjects with external oesophageal perforation. There were 49 male and two female patients of mean age 25·6 (range 11–56) years. This was less than the mean age of patients with iatrogenic internal perforation (59·5 years) seen over the same period[8].

The 51 injuries represented 33 stabbings, 17 bullet wounds and one hyperextension blunt injury (as already described[9]). The location and type of the injuries are presented in *Table 1*. *Table 2* shows the clinical findings and *Table 3* the radiological results.

Contrast oesophagography in a lateral decubitus position[10] was used in 16 patients and rigid oesophagoscopy in ten.

Table 1 *Type and location of injuries*

	No. of patients
Stab wound	
Pharynx	11
Oesophagus	
Cervical	21
Thoracic	1
Bullet wound	
Pharynx	4
Oesophagus	
Cervical	7
Thoracic	4
Abdominal	2
Hyperextension	
Junction of cervical–thoracic oesophagus	1
Total	51

Table 2 *Clinical findings suspicious of or compatible with oesophageal or pharyngeal perforation*

	No. of patients
Neck and thorax ($n = 20$)	
Surgical emphysema*	16
Odynophagia or dysphagia*	10
Haematemesis*	1
Inflammatory swelling of the neck*	1
Abdomen ($n = 2$)	
Acute abdomen†	2
Total	22

*Suspicious of perforation; †compatible with perforation

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Table 3 *Radiological investigations diagnostic of, suggestive of or compatible with oesophageal perforation*

	No. of patients
Chest radiography ($n = 19$)	
Surgical emphysema†	17
Haemopneumothorax‡	3
Widening of mediastinum‡	1
Increased distance from trachea to vertebral column‡	1
Positive oesophagography ($n = 16$)*	
Water-soluble contrast	12
Barium	2
Propyliodone	2
Total	29

*Diagnostic of perforation; †suggestive of perforation; ‡compatible with perforation

Table 4 *Indications for surgical exploration*

	No. of patients
Neck exploration ($n = 44$)*	
General indications for exploration	32
Findings suggestive or diagnostic of oesophageal perforation ($n = 38$)	
Clinical	20
Radiological	25
Endoscopic	7
Both of the above	26
Thoracotomy ($n = 6$)	
Leak in contrast study	5
Life-saving sternotomy	1
Exploratory laparotomy ($n = 2$)*	
Peritonism	2
Total	52†

*Laparotomy and cervical oesophagostomy as part of diversion–exclusion are not included; †one patient was subjected to thoracotomy and cervical exploration

Table 5 *Influence of type and site of injury on mortality*

	Stab wound	Bullet wound	Hyper-extension	Total
Pharynx	0 of 11	1* of 4	—	1* of 15
Oesophagus				
Cervical	0 of 21	3* of 7	—	3* of 28
Cervical–thoracic	—	—	1 of 1	1 of 1
Thoracic	1 of 1	0 of 4	—	1 of 5
Abdominal	—	1* of 2	—	1* of 2
Total	1 of 33	5 of 17	1 of 1	7 of 51

*Death from associated injuries

Oesophagography demonstrated the perforation in all patients but endoscopy was positive in only seven.

In 32 patients one or more of the general indications led to surgical exploration of a neck wound regardless of suspicion of oesophageal perforation (*Table 4*).

In perforation of the thoracic oesophagus the diagnosis was based on contrast oesophagography in five patients. Two patients with perforation of the abdominal oesophagus presented with an acute abdomen. Surgical emphysema was seen on radiography in seven patients with perforation of the pharynx, eight with perforation of the cervical oesophagus and two with perforation of the thoracic oesophagus.

At surgery in 18 patients the perforation was localized exactly by palpating a nasogastric tube through the gap of the perforated oesophageal wall. Use of methylene blue or following the track of the penetrating injury also facilitated its localization.

Table 5 shows mortality according to type and site of the perforation. In 45 patients with an interval from injury to operation less than 24 h, repair of the oesophagus was performed. In the majority, this was carried out with a single layer of interrupted non-absorbable sutures. Five of these patients died from associated injuries.

Six patients underwent repair after more than 24 h. One of two such patients treated by diversion–exclusion died. In four patients the oesophagus was repaired over a T tube; one of these patients died.

Of the 51 patients, 37 had 53 associated injuries of other organs, most of which had little bearing on mortality and morbidity. There were, however, five deaths resulting directly from associated trauma, four from injury to the spine and one from multiple intra-abdominal injuries. Sixteen complications occurred in 11 of the survivors: seven had oesophageal leakage, five pneumonia, two thrombophlebitis, one a neck haematoma and one a disorganized chest requiring lung decortication.

A large proportion of complications in patients who died were related to paraplegia: pneumonia (two), bed sores (two), aspiration (one), pulmonary embolism (one) and septic shock (one). Other complications unrelated to paraplegia were: pneumonia (one), leakage after T tube repair with fulminant mediastinitis (one), leakage after late repair (one), intra-abdominal sepsis (one), psychiatric problems with lack of motivation after a long convalescence (one) and malfunction of a jejunostomy (one).

Discussion

When neck exploration for penetrating trauma is planned because of positive general criteria, oesophagography is not necessary. Associated spinal injuries in the present series were the main cause of death. Those from delayed treatment were fewer. This might be attributed to the use of special surgical methods: repair with oesophageal diversion–exclusion and repair over a T tube. Repair with diversion–exclusion was associated with the problems already described.

In four patients where the delay from injury to repair had exceeded the 24-h limit by only a few hours T tube repair was used. Previous favourable reports of this method followed 'spontaneous' rupture of the Boerhaave type[7]. In the present series T tube repair was used for external penetrating injuries; the single death associated with this approach occurred in a patient treated after the development of fulminant mediastinitis[11]. This procedure should be assessed further as it has significant advantages: it is less time-consuming and does not require lengthy hospital stay with repeated surgical procedures. The method is clearly inappropriate where the tissues are extremely friable after a long delay.

There has been a trend away from non-operative conservative treatment for external penetrating injury of the oesophagus[12]. This is contrary to current practice for small iatrogenic perforation from flexible instruments. It is unclear whether simple surgical drainage of the injured area without repair of the oesophageal perforation is adequate[11].

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Case report

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Abdominal cocoon: a report of two cases

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Encasement of the bowel in a fibrous cocoon is a rare cause of intestinal obstruction[1,2] that can be part of a syndrome of generalized visceral fibrosis[2,3]. Two patients are reported, one a young man with associated liver cirrhosis, the other a woman with constrictive pericarditis and a history of taking propranolol.

Case reports

Patient 1

A 17-year-old man presented with acute intestinal obstruction. He had five previous hospital admissions for similar episodes that had settled with conservative treatment. Examination revealed a tender right paraumbilical mass. Abdominal radiography did not show obvious intestinal obstruction.

A provisional diagnosis of intermittent intussusception was made, and laparotomy was performed. The stomach and intestines were found to be encased in a thick fibrous cocoon, within which there were interloop adhesions of the intestines. Simple excision of the cocoon with lysis of the adhesions was performed.

The patient developed bleeding from oesophageal varices on the eighth day after operation; this responded to injection sclerotherapy. Liver biopsy revealed cirrhosis. The man was well on discharge.

Patient 2

A 43-year-old woman presented with abdominal pain associated with vomiting and constipation. She had had similar episodes over the previous 3 months that had resolved spontaneously. She also had orthopnoea and effort dyspnoea. The patient had been taking propranolol 40 mg twice daily for the previous 2 years for hypertension. Examination revealed raised jugular venous pressure and pulmonary oedema. There was an ill defined and tender lower abdominal mass. Radiography showed pericardial calcification and equivocal signs of intestinal obstruction.

At laparotomy the stomach, liver and intestines were found to be encased in a thick fibrous cocoon, about 0·5–2 mm thick, which was separate from the parietal peritoneum. There were soft fibrous adhesions between the encased bowel loops. The cocoon was easily peeled off, freeing the intestines. The patient made an uneventful recovery.

In both cases the excised cocoon was reported histopathologically to be a sheet of thick membranous hypocellular fibrous tissue with no evidence of inflammation or granuloma formation.

Discussion

The aetiology of abdominal cocoon remains obscure. The β-blockers have been implicated, in particular propranolol. This group of drugs lowers the adenosine 3′,5′-cyclic monophosphate: guanosine 3′,5′-cyclic monophosphate ratio which controls normal cellular proliferation; this may therefore initiate excessive proliferation[4]. Collagen production is suppressed *in vitro* by endogenous β-agonists. By interfering with this inhibition, β-blockers may lead to enhanced collagen production and subsequent fibrosis[5]. About 25 per cent of patients with sclerosing peritonitis induced by β-blockers have inflammatory involvement of another serous cavity such as the pleural space or pericardium[3], as in patient 2 with constrictive pericarditis.

The association of abdominal cocoon with liver cirrhosis has not been reported previously, and patient 1 is also unusual in being male[1].

Intestinal obstruction in these two patients was caused simply by kinking and compression of the intestines within the constricting cocoon and was completely relieved after cocoon excision. Bowel resection was unnecessary.

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Survival following microscopically confirmed radical resection of N_0 gastric cancer

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In a series of 128 patients operated on for gastric cancer, 27 satisfied microscopic criteria for radical resection. The median age of these patients was 72·3 (range 36–84) years at operation; the median hospital stay after surgery was 12·9 days. The median observation time was 3·8 years and the crude 5-year survival rate 48 per cent. Older patients did remarkably well. No significant difference was found in the number of survivors, survival–observation time or hospital stay in the age groups 55–64, 65–74 or 75–84 years. Thus, age alone should not be considered a barrier to curative surgical treatment. When the study was ended, 12 of the 27 patients who underwent microscopically confirmed radical resection were still alive; six had died from recurrent gastric cancer and nine from other causes. At 5 years after microscopically confirmed radical resection for gastric carcinoma, the gastric cancer-specific mortality rate was 23 per cent.

The age distribution of the population is changing in the West. In Denmark[1] the proportion of the population that is aged 65 years or more rose from 7 per cent of men and 8 per cent of women in 1940 to 13 and 17 per cent respectively in 1986. This has generated an interest in how well operations are tolerated by elderly patients.

Frederiksberg is an urban community of population approximately 86 000, with an over-representation of old people[2]: 18 per cent of men and 31 per cent of women are ≥65 years. Frederiksberg Hospital is the regional infirmary, to which all patients from the region are admitted.

In the West, adenocarcinoma of the stomach (excluding the oesophagogastric junction) affects mainly the elderly, and its incidence has declined over the past 40 years – in Denmark[3] from 1590 cases a year in 1943–1947 to 782 in 1978–1982. The prognosis is still poor, and considerations on this may postpone diagnosis and treatment, especially in elderly patients.

In this retrospective survey the toleration of older patients for surgery that met microscopic criteria for radical resection of gastric cancer was studied.

Patients and methods

A total of 129 patients underwent operation for primary adenocarcinoma of the stomach (other than the oesophagogastric region) during the period from January 1978 to December 1988. One patient was excluded because of concurrent cancer of the colon, leaving 128 patients with a median age at operation of 71·3 (range 36–91) years. There were 60 men (median age 68·5 (range 36–91) years) and 68 women (median age 74·5 (range 37–89) years), a male:female ratio of 0·88:1. The study was ended on 1 May 1991.

Routine practice was to perform the smallest resection consistent with a tumour-free margin of 5 cm; total gastrectomy was performed only if necessary to achieve this. All palpable lymph node metastases were excised, and when there were no palpable nodal metastases only the perigastric (group 1) lymph nodes were dissected (R_1 gastrectomy)[4].

All medical records were reviewed; most were complete and in the few cases where the histology report was missing the Institute of Pathology had a copy. At the end of the study 13 patients were still alive, with a median observation time of 2219 (range 992–3000) days, or approximately 6·1 years; 115 had died. None of the patients had emigrated, so that the time of all deaths could be confirmed from the Danish National Register, to which all Danish hospitals are connected. The cause of death was verified from the medical records in 103 patients, of whom 98 died at Frederiksberg Hospital and five at other Danish hospitals. In all those who died with proven recurrence, the cause of death was considered to have been gastric cancer, including ten patients who died at home with proven recurrence. Two patients died at home after 3·2 and 4·6 years respectively; one had not been to any hospital during this time, and the other had been hospitalized for a heart condition only. These two patients were considered to have died from other causes.

Analysis was performed with Medstat (Astra, Albertslund, Denmark), a personal computer database and a statistical package which include Kaplan–Meier life-table analysis for cumulated survival rates.

The age- and sex-matched expected survival rate based on national death statistics was estimated by the Danish Medical Research Council.

Results

A total of 68 resections were performed: five total gastrectomies and 63 other resections, of which 57 included approximately two-thirds and six only one-third of the stomach. In 60 patients the tumour was too widespread for resection; 17 underwent gastroenterostomy. Of the 68 resections, 20 were palliative, 48 macroscopically radical but only 27 radical on microscopic criteria ($N_0S_0P_0H_0$); none of the latter was a total gastrectomy. The distribution according to age and operability of the patients is shown in *Figure 1*.

The median age of the 27 patients who satisfied microscopic criteria for radical resection was 72·3 (range 36–84) years; there were 14 men and 13 women. Three patients had urgent surgery

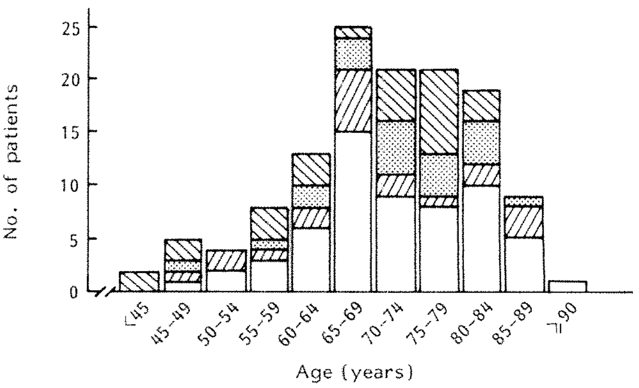

Figure 1 *Age and operability of 128 patients operated on for gastric cancer, excluding that of the oesophagogastric junction.* □, *No resection* (n = *60*); ▨, *non-radical resection* (n = *20*); ⬚, *macroscopically radical resection* (n = *21*); ▧, *microscopically confirmed radical resection* (n = *27*)

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Table 1 *Details of 27 patients undergoing microscopically confirmed radical resection for gastric cancer*

Age group (years)	Observation or survival time (days)*	Length of hospital stay (days)*	Alive	Dead: Recurrence	Dead: Other cause
≤54 (*n* = 4)	2125 (1020–2867)	8·5 (8–21)	3	1	0
55–64 (*n* = 6)	1295 (695–2670)	13·5 (9–21)	3	1	2
65–74 (*n* = 6)	1512 (18–2789)	17·0 (12–34)	2	2	2
75–84 (*n* = 11)	1328 (5–3000)	12·7 (5–27)	4	2	5
All patients	1405 (5–3000)	12·9 (5–34)	12	6	9

*Values are median (range)

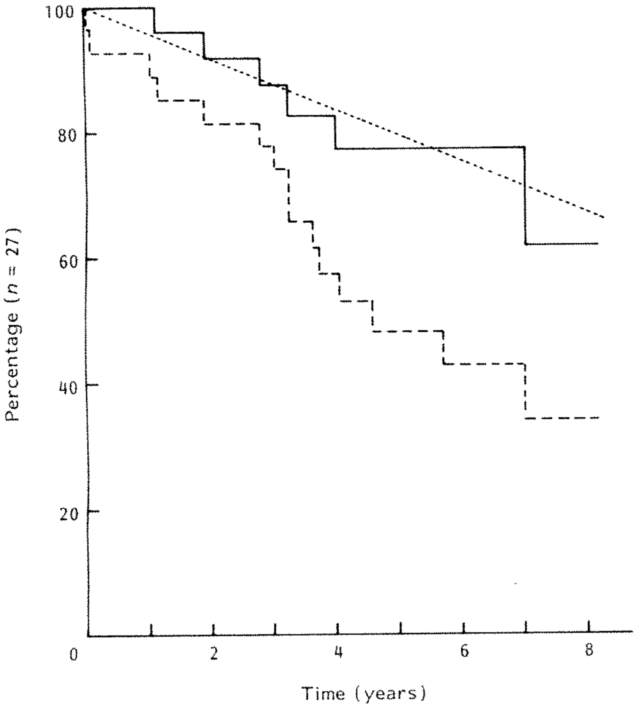

Figure 2 *Survival following microscopically confirmed radical resection in 27 patients operated on for gastric cancer, excluding that of the oesophagogastric junction.* ·····, *Age- and sex-matched expected survival rate based on the mortality rate of the Danish population;* – – –, *overall (crude) survival rate (Kaplan–Meier);* ——, *gastric cancer-specific mortality rate expressed as percentage not dead from recurrence (Kaplan–Meier; see text for details). After 5 years 11 patients were still at risk (Kaplan–Meier)*

for uncontrolled haemorrhage. Two patients died within the first 30 days after operation, resulting in a perioperative mortality rate of 7 per cent. There were no perioperative deaths among the 21 patients who had macroscopic clearance which was not confirmed microscopically.

The median observation–survival time for all patients undergoing microscopically confirmed radical resection was 1405 (range 5–3000) days, or approximately 3·8 years. Of the 27 patients, 12 are still alive with a median observation time of 2241 (range 1046–3000) days, or approximately 6·1 years, while 15 have died (including the perioperative deaths) after a median (range) survival time of 1185 (5–2564) days, or approximately 3·2 years, six from recurrence of gastric cancer (1102 (414–2564) days) and nine from other causes without known recurrence (1185 (5–2092) days). The crude survival rate was 82 per cent at 2 years, 48 per cent at 5 years and 34 per cent at 8 years (*Figure 2*).

The median length of stay in hospital after radical resection confirmed microscopically was 12·9 (range 5–34) days. *Table 1* shows the length of stay, the observation–survival time and cause of death in different age groups.

Discussion

The present survey has the disadvantage of all retrospective surveys: the results are poor from the standpoint of current technical abilities. All patients with gastric cancer are now evaluated using ultrasonography and/or computed tomography (CT) before elective operation, and examination of frozen sections of lymph nodes and resection margins is used to help determine the extent of resection. However, ultrasonography and CT were available in the department only during the last years of the study period, and frozen-section microscopy became routine only after that period. Given the small number of patients with gastric cancer operated on each year, it is too early to evaluate the results of these improvements. A reduction in the number of unnecessary laparotomies is to be expected, as well as an improvement in peroperative staging and thus in the outcome of operation for node-positive gastric cancer. However, routine practice is still to perform only R_1 gastrectomy in node-negative gastric cancer.

In the present series of 128 patients operated on for gastric cancer, 27 (21 per cent) underwent radical resection based on microscopic criteria. As in other Western series[5–12], at the time of diagnosis most of the tumours had spread beyond curative treatment. The perioperative mortality rate among all intended curative resections was 4 per cent (two of 48), which is similar to rates from other Western surveys[5–7,10,13–16]. Both of the perioperative deaths were in the first half of the period. The patients were aged 72 and 80 years; the latter was operated on urgently because of severe haemorrhage, and both had severe concurrent disease.

The toleration of elderly patients to operation is often evaluated by comparing the results in those above and below the age of 70 years[13,14,17]. However, this age limit seems arbitrary and, at least in the West, outdated. The older patients in this study did remarkably well. The numbers were small, but χ^2 analysis showed no significant difference in observation–survival time, hospital stay or number of survivors in the age groups 55–64, 65–74 and 75–84 years. Other Danish[18] and Swedish[19] surveys have also found that patients above 80 years tolerate operation well.

Different statistical methods have been used to evaluate the results after operation for gastric cancer. Most surveys give crude survival rates. The crude 5-year survival rate (Kaplan–Meier) after microscopically confirmed radical resection in the present study was 48 per cent, which is comparable to the rates of 24–45·5 per cent reported from other Western centres[5,6,9,10,14,16], including perioperative deaths.

The use of crude survival rates makes the prognosis seem even poorer, because many of the patients are old. Of the 27 patients with microscopically confirmed clearance in the present study, 15 died after a median survival time of 3·2 years. However, only six died from recurrent gastric cancer, while nine died from other causes. This problem may be solved by estimation of cancer-specific mortality by Kaplan–Meier life-table analysis, counting patients who died from causes other than recurrence as 'lost to follow up'. In the present survey, 5 years after the operation 77 per cent of patients with microscopically confirmed clearance had not died from recurrent gastric cancer, giving a cancer-specific 5-year mortality rate of 23 per cent.

In conclusion, 75–84-year-old patients did as well as those aged 65–74 or 55–64 years following microscopically complete R_1 resection for gastric cancer. When considering curative treatment, age alone should be no barrier to surgery. Instead of crude survival rates, it is suggested that cancer-specific mortality rates be used to determine the outcome of operation for gastric cancer.

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Extensive *versus* limited lymph node dissection for gastric cancer: a comparative study of 320 patients

To compare extensive with limited lymph node dissection in the surgical treatment of gastric cancer, 320 patients undergoing gastric resection during 1981–1990 were divided into two groups. Although patients undergoing extended lymphadenectomy (n = *157*) *had a longer operating time* (P = *0·0001*) *and a greater intraoperative blood transfusion requirement* (P = *0·009*) *than those receiving limited dissection* (n = *163*), *the incidence of postoperative complications* (*22·3* versus *28·2 per cent,* P = *0·13*) *and the hospital mortality rate* (*3·8* versus *7·4 per cent,* P = *0·12*) *were similar in the two groups. The 5-year survival rate after curative resection* (*117 and 121 patients after extensive and limited lymph node dissection respectively*) *was 65·4* versus *50·1 per cent* (P = *0·01*)*: 85·9* versus *82·2 per cent for stage I disease* (P = *0·60*), *66·1* versus *57·8 per cent for stage II* (P = *0·82*) *and 48·7* versus *29·8 per cent for stage III* (P = *0·02*). *Multivariate analysis using the Cox model showed that the extent of lymphadenectomy was an independent prognostic factor for survival* (P = *0·01*). *The results support the value of extensive lymph node dissection in the surgical treatment of gastric carcinoma.*

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Controversy still surrounds the value of extensive regional lymph node dissection in the curative treatment of gastric adenocarcinoma.

The R_2 and R_3 types of gastrectomy are routinely used in most operations for gastric cancer in Japan and, depending on the location of the primary tumour, these methods include removal of n2 and n3 as well as the perigastric (n1) lymph nodes[1–4]. This contrasts with surgical practice in the UK and USA where R_1 gastrectomy predominates and only the perigastric nodes are removed during gastric resection[5,6]. Resistance in the West to the use of more radical types of gastrectomy is based on uncertainty of the value of such procedures and on the unfavourable results of such operations in the USA 20 years ago[7].

The aim of the present study was to compare the results of extended lymphadenectomy with those of limited lymph node dissection in the surgical treatment of gastric carcinoma.

Patients and methods

A retrospective cohort study was carried out on 320 patients with histologically proven adenocarcinoma of the stomach who underwent resection during 1981–1990. Patients were admitted under the care of one of two surgical teams, depending on the availability of beds. The two teams adopted different policies: one routinely performed extended lymphadenectomy and the other limited lymph node dissection.

The group undergoing extensive dissection consisted of 157 patients operated on by one senior surgeon. Of these patients, 94 underwent total gastrectomy with R_3 lymphadenectomy as described by the Japanese Research Society for Gastric Cancer[8]. The entire greater omentum, superior leaf of the mesocolon, pancreatic capsule, lesser omentum, spleen and all perigastric nodes (nos 1–6 according to the Japanese classification) were removed *en bloc* with the stomach; lymphadenectomy was performed in the infraduodenal and supraduodenal areas, along the hepatic pedicle (node 12) and retropancreatic region (node 13), and along the common hepatic (node 8), coeliac (node 9), mesenteric (node 14) and splenic (node 11) arteries. The left gastric artery was ligated at its origin. The remaining 63 patients in this group underwent distal subtotal gastrectomy and R_2 lymphadenectomy extended to the hepatic pedicle and retropancreatic nodes.

The group undergoing limited lymph node dissection consisted of 163 patients who underwent R_1 gastrectomy during the same period. The operation was performed by one of two senior surgeons. Total and distal subtotal gastrectomy were performed in 63 and 100 patients respectively. Lymphadenectomy included only the perigastric nodes in 105 patients (64·4 per cent) and some n2 nodes, with staging intent, in 58 (35·6 per cent).

Tumour location and gross appearance, histological type according to Laurén, margins of clearance in the resection specimen, depth of invasion and regional lymph node involvement were recorded.

Among patients undergoing extended lymphadenectomy, resection was judged to be 'absolutely curative' ($H_0 P_0 S_{0-2} N^+ < R$ according to Japanese nomenclature) in 122 cases and 'relatively curative' ($H_0 P_0 S_{0-2} N^+ = R$) in 13 cases. Eight patients underwent 'relatively non-curative' resection and 14 'absolutely non-curative' resection.

Among patients undergoing limited lymph node dissection, tumour resection was judged to be curative in 128 cases when no grossly visible tumour tissue (metastatic and/or lymph node involvement) had been left and resection margins were histologically free from disease. Some 35 patients therefore underwent palliative resection.

The length of operation, intraoperative blood loss, postoperative morbidity rate, hospital mortality rate and 5-year survival after curative resection were recorded in both groups.

Statistical analysis

Statistical analysis was carried out using the BMDP package (BMDP Statistical Software, Los Angeles, California, USA). Results are expressed as mean(s.d.). The significance of differences between means was assessed using Student's *t* test and comparison of the rate of occurrence of events using Fisher's exact test. Survival curves were constructed according to the actuarial life-table method. Only patients undergoing curative resection were included, after exclusion of operative deaths. Therefore, survival after curative resection was studied in 238 patients: 117 after extensive and 121 after limited lymph node dissection. Nine patients (3·8 per cent) were lost to follow-up: five (4·3 per cent) of those undergoing extended lymphadenectomy and four (3·3 per cent) of those undergoing limited dissection.

A total of 146 patients (61·3 per cent) were followed for 5 years after operation. Survival curves were compared using the Mantel–Cox test[9].

Variables shown to be prognostically significant by univariate

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Table 1 *Details of patients*

	Lymph node dissection	
	Extensive ($n = 157$)	Limited ($n = 163$)
Mean(s.d.) age (years)	60·4(11·3)	61·6(11·0)
Sex ratio (M:F)	100:57	114:49
Tumour stage		
Early	20	20
Advanced	137	143
Tumour location		
Lower third	75	83
Middle third	51	51
Upper third	31	29
Gross tumour appearance		
Ulcerating	72	80
Infiltrating	59	50
Fungating	26	33
Histological type		
Diffuse	69	85
Intestinal	82	60
Undetermined	6	18
Tumour node metastasis stage		
IA	15	19
IB	23	10
II	39	35
IIIA	33	50
IIIB	18	32
IV	29	17
Gastric resection		
Total	94	63
Subtotal	63	100

Table 2 *Postoperative complications*

	Lymph node dissection	
Complication	Extensive	Limited
Wound infection	3	8
Anastomotic leakage	6 (1)	9 (3)
Intra-abdominal abscess	6 (3)	5 (2)
Abdominal wound dehiscence	1	0
Duodenal stump dehiscence	0	3 (1)
Pancreatic fistula	1	2
Haemorrhage	1 (1)	1 (1)
Intestinal obstruction	0	1
Necrotizing pancreatitis	0	1 (1)
Pneumonia	8	5
Acute respiratory distress syndrome	0	3 (3)
Pulmonary embolism	3	0
Myocardial infarction	1 (1)	1 (1)
Other	5	7
Total	35	46

Values in parentheses are numbers of postoperative deaths

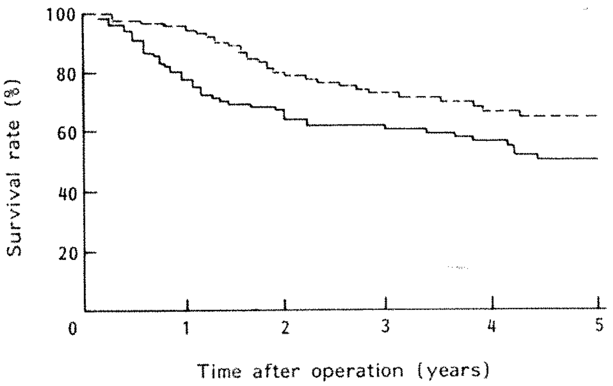
analysis were entered into a multivariate model. Multivariate analysis was applied using the Cox regression proportional hazards model[10].

Results

Age–sex distribution and pathological features were similar in the two groups (*Table 1*). The mean(s.d.) number of lymph nodes dissected per operative specimen was 37·0(22·4) in the patients undergoing extended lymphadenectomy and 12·4(8·9) in those receiving limited dissection ($P = 0·0001$). Histological examination revealed nodal involvement in 93 patients (59·2 per cent) and 105 patients (64·4 per cent) in the extensive and limited dissection groups respectively ($P = 0·2$); there were 56 (35·7 per cent) and 73 (44·8 per cent) with positive n1 nodes, and 18 (11·5 per cent) and 32 (19·6 per cent) with n2 involvement. In 19 patients (12·1 per cent) undergoing extensive dissection n3 nodes were involved.

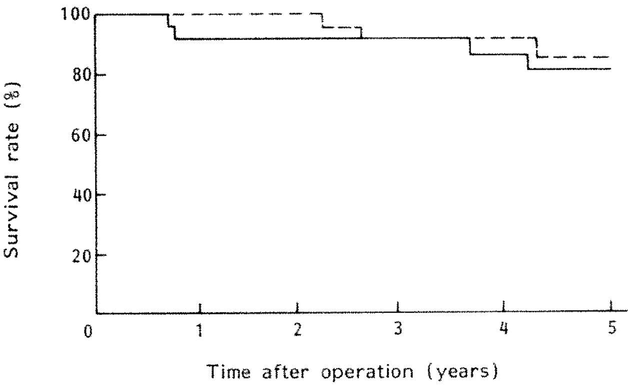
Morbidity and mortality rates

The mean(s.d.) operating time was 269(82) min for extended lymphadenectomy and 220(78) min for limited dissection ($P = 0·0001$). The mean(s.d.) intraoperative blood transfusion requirement was 578(481) and 438(456) ml respectively ($P = 0·009$). The incidence of postoperative complications



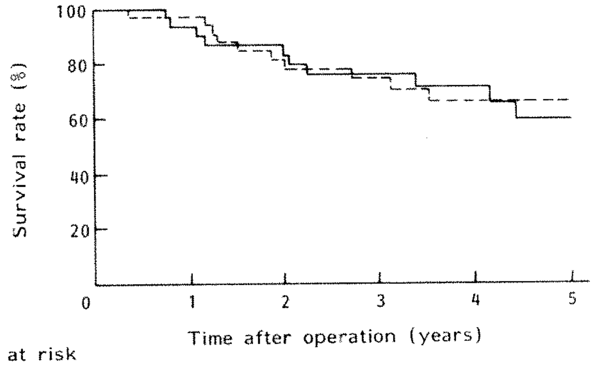
No. at risk	0	1	2	3	4	5
Extensive	117	99	73	55	41	36
Limited	121	89	63	54	40	27

Figure 1 *Survival curves of 238 patients undergoing curative resection, excluding operative deaths. ---, Extensive lymph node dissection; —, limited lymph node dissection.* P = *0·01 (Mantel–Cox test)*



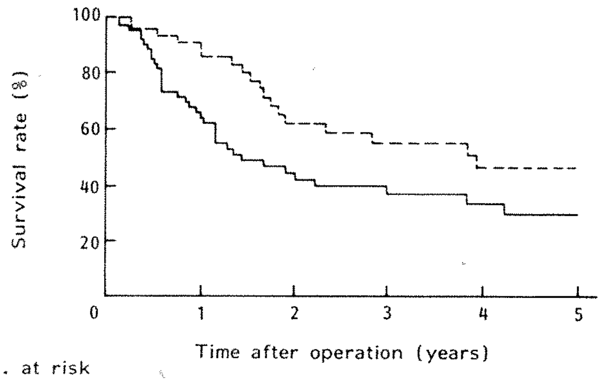
No. at risk	0	1	2	3	4	5
Extensive	36	30	27	21	16	13
Limited	28	24	20	20	17	14

Figure 2 *Survival curves of 64 patients with stage I gastric carcinoma, excluding operative deaths. ---, Extensive lymph node dissection; —, limited lymph node dissection.* P = *0·60 (Mantel–Cox test)*



No. at risk	0	1	2	3	4	5
Extensive	36	33	25	19	14	13
Limited	31	28	24	19	13	7

Figure 3 *Survival curves of 67 patients with stage II gastric carcinoma, excluding operative deaths. ---, Extensive lymph node dissection; —, limited lymph node dissection.* P = *0·82 (Mantel–Cox test)*



No. at risk						
Extensive	45	36	21	15	11	10
Limited	62	37	19	15	10	6

Figure 4 *Survival curves of 107 patients with stage III gastric carcinoma, excluding operative deaths. – – –, Extensive lymph node dissection; ——, limited lymph node dissection.* P = *0·02 (Mantel–Cox test)*

Table 3 *Univariate analysis of clinical and pathological variables after curative resection of gastric carcinoma in 238 patients*

Variable	No. of patients	5-year survival rate (%)	*P**
Age (years)			
<60	107	63·6	0·09
≥60	131	52·2	
Sex			
M	161	57·6	0·92
F	77	57·5	
Tumour location			
Lower third	114	63·8	0·008
Middle third	71	60·9	
Upper third	53	38·9	
Gross tumour appearance			
Ulcerating	115	65·3	0·06
Infiltrating	77	48·2	
Fungating	46	55·3	
Histological type			
Diffuse	102	53·4	0·25
Intestinal	118	58·8	
Undetermined	18	69·9	
Tumour node metastasis stage			
IA	32	95·6	<0·0001
IB	32	72·7	
II	67	62·7	
IIIA	68	40·2	
IIIB	39	33·2	
Gastric resection			
Total	125	57·9	0·82
Subtotal	113	54·4	
Lymph node dissection			
Limited	121	50·1	0·01
Extensive	117	65·4	

*Fisher's exact test

(*Table 2*) was similar in the two groups (22·3 *versus* 28·2 per cent, $P = 0·13$).

The hospital mortality rate was 3·8 per cent after extensive and 7·4 per cent after limited lymph node dissection ($P = 0·12$).

Survival

The 5-year survival rate after curative resection was 65·4 per cent for extended lymphadenectomy and 50·1 per cent for limited dissection ($P = 0·01$). The rates were 85·9 *versus* 82·2 per cent for stage I disease ($P = 0·60$), 66·1 *versus* 57·8 per cent for stage II ($P = 0·82$), and 48·7 *versus* 29·8 per cent for stage III ($P = 0·02$) (*Figures 1–4*).

When applied to all patients undergoing curative resection, univariate analysis showed that poor survival was closely related to the site of the primary lesion, tumour node metastasis (TNM) stage and the extent of lymphadenectomy. In contrast, no significant differences were found with regard to age, sex, gross tumour appearance, histological type and extent of gastric resection (*Table 3*).

Table 4 *Independent prognostic variables identified by a Cox proportional hazards model using the covariates in* Table 3

Prognostic variable	Hazards ratio	*P**
Lymph node dissection		
Limited *versus* extensive	0·55 (0·35–0·87)	0·01
Stage		
II *versus* I	2·76 (1·17–6·53)	0·02
III *versus* I	6·54 (2·95–11·48)	<0·0001
Tumour location		
Upper third *versus* middle plus lower thirds	1·87 (1·15–3·04)	0·01

Values in parentheses are 95 per cent confidence intervals. *Mantel–Cox test

Of the three factors found to be prognostically significant by univariate analysis, the Cox multivariate model confirmed that all three were independent predictors of death from the disease (*Table 4*). Location of the tumour in the upper third of the stomach, progression of disease into the gastric wall and regional lymph nodes, and lymphadenectomy limited to the perigastric nodes were associated with a shorter survival time and higher risk of death from gastric cancer.

Discussion

The need to perform extensive lymph node dissection in the surgical treatment of gastric cancer remains controversial. Many reports have suggested an aggressive procedure ($R_{2/3}$ gastrectomy) based on the assumption that the more extensive removal of lymph nodes permits a more accurate staging and a better prospect of cure[11–13]. However, other investigators have recommended a less aggressive approach. The main argument for R_1 gastrectomy is the much lower postoperative morbidity and mortality rates with no statistically different survival rate when compared with results of extended lymphadenectomy in several reports[7,14].

The aim of the present study was to compare extended lymphadenectomy with limited nodal dissection in the surgical treatment of gastric carcinoma. As far as early postoperative results are concerned, this study confirms that the more extensive dissection leads to a longer operating time and greater blood loss[14]; however, no differences were observed in postoperative morbidity and mortality rates between the two procedures. All the extensive dissection operations were performed by the same senior surgeon: this might explain the lower than expected incidence of postoperative complications in this group of patients. Nevertheless, the results suggest that extended lymphadenectomy, when performed in a standardized manner, does not significantly increase complication and mortality rates compared with limited dissection.

Long-term results after curative resection show the survival advantage of extensive over limited lymphadenectomy, a difference that was more marked when patients with stage III disease were considered separately. It must be underlined that lymph node involvement might be underestimated in patients undergoing limited dissection in comparison with those receiving extended lymphadenectomy, because of the presence of undetected n3 metastases. This possibility does not affect the overall finding of reduced survival in patients who underwent limited dissection, as it is reasonable to assume that more extensive lymphadenectomy might have resulted in surgical cure of some patients with undetected micrometastases in those undergoing limited dissection.

Multivariate analysis using the Cox model confirmed the extent of lymphadenectomy as an independent predictor of survival in patients undergoing curative resection. Statistical analysis showed that, even though there are predetermined factors that govern survival, such as location of the tumour and TNM stage, the surgeon's choice and manner of execution of surgery can have a significant effect on prognosis.

In conclusion, despite the unfavourable results of previous Western studies comparing extensive with limited lymph node dissection, the present data clearly show the safety and efficacy of extended lymphadenectomy in the surgical treatment of gastric cancer. The results are in agreement not only with those of Japanese authors but also with reports of $R_{2/3}$ gastrectomy recently performed outside Japan[15–17] and support the efficacy of extended lymph node dissection in the surgical management of gastric carcinoma.

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Case report

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Small bowel prolapse and incarceration caused by a vaginal ring pessary

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Incarceration of the intestine is always a surgical emergency. Most frequently, it occurs into external or internal hernias. An unusual case of small bowel incarceration into a vaginal ring pessary is reported.

Case report

A 72-year-old woman was seen in the emergency room with a 2-h history of acute abdominal pain and transvaginal prolapse of the bowel, which had developed immediately after a strong fit of coughing. The patient had undergone transvaginal hysterectomy and colpoperineoplasty 10 years previously for vaginouterine prolapse. A soft rubber vaginal ring pessary of 5·5 cm diameter had been inserted 5 years later because the woman had developed a recurrent rectocystocele but had refused further operation. Periodic follow-up examinations had always been unremarkable.

On clinical examination bowel loops were visible, protruding externally from the vagina (*Figure 1*). The blood pressure was 200/130 mmHg and the heart rate 88 beats/min. The abdomen was tender with no guarding and bowel sounds were decreased. The white blood cell count was slightly raised at $12 \cdot 5 \times 10^9$/l. Plain abdominal radiography showed distended small bowel loops but no air–fluid levels.

At emergency laparotomy, exploration of the pelvis revealed perforation of the vaginal stump and incarceration of the terminal ileum into the vaginal pessary. A 45-cm segment of ischaemic bowel was removed, and end-to-end ileoileal anastomosis performed. The vagina was stabilized by fixation to remnants of the sacrouterine and round ligaments, and the vaginal defect was closed.

The patient had an uneventful postoperative course and was discharged on day 11.

Discussion

There is agreement that definitive treatment of genital prolapse should consist of extirpative or reconstructive surgery, because this is well tolerated even in elderly patients[1]. Vaginal supportive devices should be restricted to patients who refuse or are awaiting operation, since their use is frequently associated with ulceration of the mucous membrane, vaginal discharge and pruritus[2]. Incarceration or perforation of the cervix or parts of the bladder are rare complications that result mainly from neglect[1].

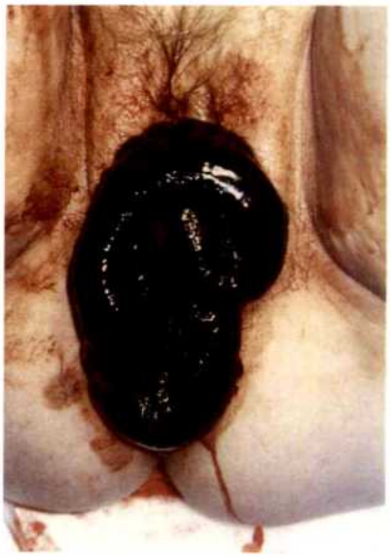

Figure 1 *Transvaginal bowel prolapse*

Intestinal obstruction caused by a vaginal pessary is a clinical rarity. A literature review of this complication revealed two reports of compression ileus but not a single instance of incarceration and transvaginal bowel prolapse. Seling and Lindenfelser[3] described a patient in whom a retrovaginal small bowel loop was compressed by a ring pessary; a similar case was reported by Lukowski[4]. In the present patient, intestinal obstruction and bowel prolapse resulted from perforation of the vaginal stump and incarceration into the ring of the pessary. This was clearly related to the preceding hysterectomy, since the uterus with its fixation in the pelvis acts as a barrier between the abdominal cavity and vagina.

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Factors associated with early discharge after inguinal hernia repair in 500 consecutive unselected patients

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The feasibility of discharge within 48 h of surgery was evaluated in 500 consecutive men with unilateral uncomplicated non-recurrent inguinal hernia. Fifty-nine patients were unsuitable for short-stay surgery on medical or social grounds. Of 411 patients suitable for early discharge, 107 stayed longer than 48 h. Early discharge was declined by 84 otherwise suitable patients and contraindicated because of local or general complications in 42. A total of 304 patients were discharged within 48 h; 1-day surgery was performed in 51 patients. Employment, low physical requirements, a lower age and fewer than two medical risk factors were associated with feasible and successful short-stay surgery. These factors may not be independent variables.

The feasibility of early discharge from hospital after inguinal hernia repair in selected patients was established 30 years ago[1]. The question remains of how to select patients for early discharge, particularly when financial incentives are not likely to promote acceptance[2]. Accurate prediction of the delay to discharge might optimize the use of hospital beds. The present study was conducted to determine the relative predictive values of medical fitness, social support and patient acceptance in the feasibility of early discharge after inguinal hernia repair. The objective was discharge within 48 h of surgery.

Patients and methods

Over an 18-month period, 500 consecutive male patients aged 16 years or over were seen in the outpatient departments of 17 surgical centres of two French associations for surgical research. All hernias were inguinal, unilateral, uncomplicated and non-recurrent. At the initial interview, based on the referral letter from the general practitioner and/or information from the patient concerning medical history and social conditions, the consultant surgeon decided whether the patient was suitable for short-stay surgery. Social and medical assessment variables are shown in *Table 1*. Suitable patients were asked to stay 48 h or less after surgery; they could accept or decline this proposition.

The surgical team chose the type of anaesthesia and method of repair. Each patient was assessed from surgery until discharge with particular reference to the wound, and possible local and general complications. The date of discharge and reason for any delay beyond the proposed postoperative stay were recorded. An outpatient visit after 1 month was used to assess late complications.

Table 1 *Social and medical variables used in assessment*

Social
- Employment*
- Distance from home to hospital
- Housing conditions (poor accommodation, inadequate domestic support)
- General practitioner
- Availability of home nurse care

Medical (score 1 for each)
- Chronic respiratory disease
- Smoking more than ten cigarettes per day
- Chronic constipation
- Dysuria
- Anticoagulant therapy
- Other associated medical or surgical conditions

*Graded according to physical requirements from 1 (sedentary work) to 4 (heavy physical work)

Comparisons between group means were made using Student's t test; χ^2 with Yates' correction or Fisher's exact test, as appropriate, were used for evaluation of qualitative variables.

Results

The results are summarized in *Figure 1*. Delayed discharge was anticipated on medical or social grounds and/or because of patient refusal in 89 patients (18 per cent). Details of 411 patients of mean(s.e.m.) age 54(15) (range 16–89) years admitted for short-stay surgery are given in *Table 2* and postoperative complications in *Table 3*. In total, 107 patients remained in hospital for more than 48 h. Early discharge was refused by 103 patients either before ($n = 42$) or after ($n = 61$) operation; patient refusal was the single reason for delayed discharge in 30 patients before and in 54 after operation. A total of 56 local and 24 general complications were diagnosed while the patients were in hospital, delaying discharge in 42 patients. Local complications did not occur significantly more frequently after local anaesthesia (29 of 229; 13 per cent) than after epidural or general anaesthesia (27 of 182; 15 per cent). On the other hand, general complications were more frequent after epidural or general anaesthesia (16 of 182 *versus* eight of 229; $P < 0\cdot05$).

Factors associated with the feasibility and success of short-stay surgery are given in *Table 4*. Only the medical risk score differed between the patients with delayed discharge and those for whom early discharge was not feasible. Having no general practitioner was associated with a lower medical risk ($P < 0\cdot02$); of 66 patients without a practitioner, 47 had no medical risk factors and 19 had only one. Of 304 patients discharged, 165 (54 per cent) were operated on under local anaesthesia, as were 64 of 107 (60 per cent) with delayed discharge (P not significant). Age and employment were not independent variables: mean(s.d.) age was no different when employed patients discharged within 48 h ($n = 201$) were compared with those with delayed discharge ($n = 45$) at 45(11) *versus* 46(11) years respectively. In unemployed patients, however, lower age was associated with early discharge

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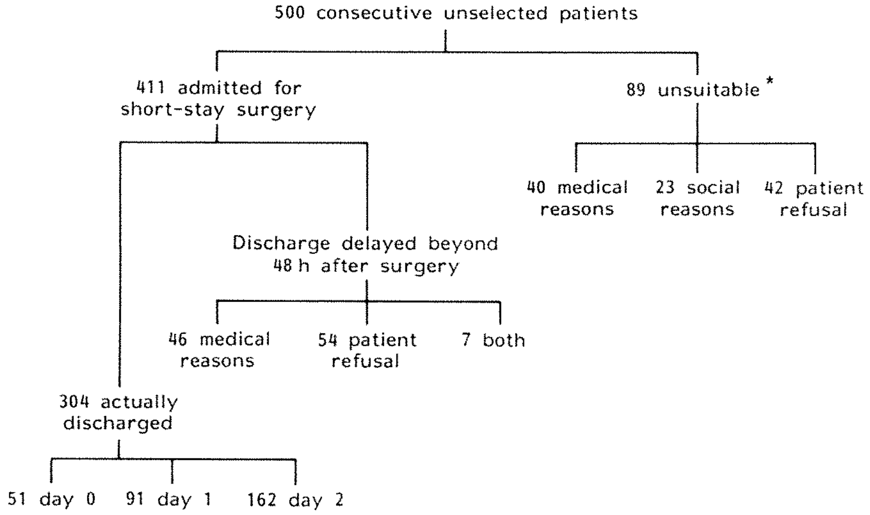

Figure 1 *Distribution of study population. *Sixteen patients had more than one reason*

Table 2 *Characteristics of 411 patients admitted for short-stay surgery*

	No. of patients
Shouldice herniorrhaphy	370 (90)
Anaesthesia	
Local	229 (56)
Epidural	71 (17)
General	111 (27)
Complications	
In hospital	
Local	48 (12)
General	16 (4)
Both	8 (2)
Late	25 (6)

Values in parentheses are percentages

Table 3 *Complications in 411 patients admitted for short-stay surgery*

	No. of cases
In hospital	
Local	
Wound haematoma	36
Wound inflammation	10
Wound infection	5
Scrotal oedema	5
General	
Chest infection	7
Urinary retention	3
Persisting pyrexia > 38°C	5
Postoperative medical problem	9
Late	
Persisting pain	17
Oedema or haematoma	5
Groin anaesthesia	1
Wound disruption	2

Table 4 *Factors associated with feasibility and success of short-stay surgery*

	Early discharge not feasible	Early discharge feasible	
		Discharge delayed	Actually discharged
No. of patients	89	107	304
Mean(s.d.) age (years)	60(16)	60(16)	50(14)‡
Employment*	37 (42)	45 (42)	201 (66)‡
Medical risk factor score*			
0	29 (33)	55 (51)	201 (66)
1	31 (35) †	31 (29)	81 (27) ‡
2	29 (33)	21 (20)	22 (7)
No general practitioner*		10 (9)	56 (18)†
Complication in hospital*			
Local		28 (26)	28 (9)§
General		21 (20)	3 (1)§

*Values in parentheses are percentages. †$P < 0{\cdot}05$; ‡$P < 0{\cdot}01$; §$P < 0{\cdot}001$ (*versus* discharge delayed, χ^2 test)

Table 5 *Relationship between age, medical risk factors and feasibility of short-stay surgery*

	Early discharge not feasible	Early discharge feasible	
		Discharge delayed	Actually discharged
Medical risk factor score			
0	54(18)	57(16)	48(15)†
1	62(11)	62(16)	53(15)*
2	66(12)	67(14)	62(10)

Values are mean(s.d.) age in years. Numbers of patients according to each medical score are given in *Table 4*. *$P < 0{\cdot}01$; †$P < 0{\cdot}001$ (*versus* discharge delayed, χ^2 test)

($n = 103$) compared with those with declined or delayed discharge ($n = 62$): mean(s.d.) 60(15) *versus* 70(14) years respectively ($P < 0{\cdot}001$). In the overall population lower age was associated with early discharge only in patients with a medical risk score <2 (*Table 5*).

Fifty-one patients were discharged the evening after operation (defined as discharge on day 0 or ambulatory surgery). Factors associated with ambulatory surgery are reported in *Table 6*.

The predictive values of factors associated with early discharge are reported in *Table 7*. The most accurate prediction of early discharge was achieved in the group of employed patients with low physical requirements. These criteria detected only 134 of 304 patients (44 per cent) accepting and going on to receive short-stay surgery.

Housing conditions, distance from home to hospital and availability of home nurse care were not discriminant factors in any of the groups compared.

Table 6 *Factors associated with ambulatory surgery (discharge on day 0) compared with discharge on day 1 or 2*

	Discharge on day 0	Discharge on day 1 or 2
No. of patients	51	253
Mean(s.d.) age (years)	51(16)	49(11)
Employment grade*		
1 or 2	26	91
3 or 4	15	69
Total	41 (80)	160 (63)†
Medical risk factor score*		
0	43 (84)	158 (62) ‡
1	4 (8)	77 (30)
2	4 (8)	18 (7)
Local anaesthesia*	48 (94)	115 (45)§
Complication in hospital*		
Local	1	26♯
General	1	3♯

*Values in parentheses are percentages. †$P < 0{\cdot}02$; ‡$P < 0{\cdot}001$; §$P < 0{\cdot}001$; ♯$P = 0{\cdot}08$ (χ^2 and Fisher's exact tests)

Table 7 *Predictability of early discharge*

	No. of patients	Early discharge feasible	Actually discharged
Total population	500	411 (82)	304 (74)
Medical risk factor score			
<2	428	368 (86)	282 (77)
0	285	256 (90)	201 (79)
In employment	283	246 (87)	201 (82)
Grade 1 or 2	157	134 (85)	117 (87)
Grade 3 or 4	126	112 (89)	84 (75)
Medical risk factor score 0	183	168 (92)	141 (84)
Employment grade 1 or 2	102	92 (91)	80 (87)
Employment grade 3 or 4	81	76 (94)	61 (80)

Values in parentheses are percentages

Discussion

Given certain medical and/or social prerequisites, short hospital stay for hernia repair is technically feasible and medically safe[1,3-5]. Acceptance of this policy is dependent on the patient in social systems of reimbursement for hospital care where direct costs are not conducive to promoting acceptance[2]. Patient acceptance and the medical decision had the same weight in determining the feasibility of short-stay surgery in the present study. Accurate prediction of the delay to discharge is necessary to optimize the use of hospital beds, particularly when day-case surgery is performed in centres without day-bed units. As earlier series referred to preselected patients, the definition of factors associated with this prediction was missing. Factors such as domestic support and medical services[6], chronic respiratory disease[7], chronic cough and bladder outflow obstruction[8] have been identified as important variables but employment has never been evaluated. Professional physical requirements influenced the success of short-stay surgery in the present study. The importance of the work variable was underestimated before surgery by consultant surgeons, who paradoxically anticipated short-stay surgery more often in the group with high physical employment requirements (*Table 7*). The 61 per cent rate of patients leaving hospital within 48 h of operation compares favourably with that of 23 per cent reported by Cannon *et al.*[6].

In the present study local anaesthesia was associated with successful ambulatory surgery (*Table 6*). As the technique of anaesthesia was not randomized, it was not possible to determine a causal relationship. The indication of local anaesthesia might refer, in the minds of the patient and/or surgeon, to an acceptance of, or a motivation for, early discharge. Local, epidural and general anaesthesia for standard inguinal herniorrhaphy have already been compared in a randomized controlled trial[9]; there were no significant differences in the groups. In the present study general complications occurred more frequently after epidural or general anaesthesia ($P < 0{\cdot}05$) and contraindicated early discharge in 21 patients (*Table 4*). Local complications were not related to the type of anaesthesia. Of the 56 patients with local complications, 28 had a delayed discharge (*Table 4*), underlining the importance of surgical skill in successful short-stay surgery. These results were obtained in surgical centres without structured day-care units. The study provides an objective basis for investment in such units and for the evaluation of their efficiency.

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Liver resection with normothermic ischaemia exceeding 1 h

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A retrospective study was made of 34 patients who underwent major liver resection with a single period of vascular occlusion exceeding 60 min. The liver remnant was normal in all cases. Vascular occlusion was achieved by continuous portal triad clamping (15 patients), hepatic vascular exclusion (15) or a sequential combination of both procedures (four). Liver cooling was not used. The mean(s.e.m.) duration of continuous normothermic liver ischaemia was 73·6(2·5) (range 60–127) min. The mean(s.e.m.) amount of blood transfused during operation was 5·3(0·8) units packed red cells. There were no deaths after surgery and the postoperative course was uneventful, or limited to asymptomatic pleural effusion, in 18 patients. Three patients suffered postoperative bleeding necessitating further surgery and one of these required reintervention for a prolonged bile leak. Four patients had transient liver failure that resolved spontaneously within 15 days. There was a 13-fold increase in serum transaminase activities and the proaccelerin level was 45 per cent that of normal on day 1 after operation. These changes were returning to normal levels within 15 days. Continuous vascular occlusion during major liver resection is a useful manoeuvre that may be performed safely on normal hepatic parenchyma for up to 90 min.

Temporary vascular occlusion has been proposed as a technique to decrease bleeding during liver surgery[1,2]. This reduction is desirable as the amount of blood transfused during operation has a major bearing on the postoperative course[1–3].

In the early 1960s it was believed that the human liver tolerated normothermic ischaemia poorly and that temporary portal triad clamping for >15 min was hazardous[4]. This principle has been challenged by studies from the authors' department[1,5,6] and other centres[2,7–10], and it is now accepted that hepatic vascular occlusion may be performed for up to 60 min without major detrimental effects.

Advances in the field of liver surgery towards more complex and extensive hepatic resection have raised the need for longer periods of vascular occlusion. Nevertheless the maximal advisable duration of vascular clamping and consequent liver ischaemia in humans remains unknown.

To determine the effects of prolonged continuous normothermic ischaemia on liver parenchyma, the clinical records of 34 patients who underwent hepatectomy performed with a single period of vascular occlusion exceeding 60 min were reviewed retrospectively. Tolerance of the liver to prolonged normothermic ischaemia was assessed by analysis of the postoperative outcome and biochemical changes.

Patients and methods

Patients

Between January 1981 and July 1991, 459 patients underwent liver resection in the authors' department, and a review was made of 34 (7·4 per cent) of these in whom hepatectomy had been performed with a single period of vascular occlusion lasting ≥60 min. All 34 patients had tumours in an otherwise healthy liver. Patients with cirrhosis, or fatty or cholestatic changes of the liver remnant were excluded.

There were 11 women and 23 men, with a mean(s.e.m.) age of 54(2) (range 34–75) years. According to the American Society of Anesthesiologists' classification[11], 21 patients were grade I, 11 were grade II and two were grade III. The indication for resection was secondary liver tumour in 26 patients and benign disease in eight (*Table 1*).

Preoperative management

For patients with malignant disease, preoperative investigation included physical examination, chest radiography and endoscopy, when appropriate, to exclude extrahepatic disease. Thoracic computed tomography was performed on patients later in the series. Preoperative blood investigations included coagulation tests (prothrombin and proaccelerin levels), and estimation of serum alanine transaminase (ALT) and asparate transaminase (AST), bilirubin, serum alkaline phosphatase, creatinine, albumin and total protein.

Surgical technique

Operative procedure. The abdomen was opened through a bilateral subcostal incision. In three patients a thoracic extension was necessary, either because of suspected involvement of the hepatocaval confluence or because of the existence of a large posterior tumour. The liver was mobilized by division of its ligaments. Dissection of the inferior vena cava below and above the liver was performed if hepatic vascular exclusion was already planned, but was postponed in other cases. The

Table 1 *Indications and extent of liver resection in 34 patients*

	No. of patients
Malignant disease	
Secondary colorectal neoplasm	23
Secondary carcinoid neoplasm	2
Secondary squamous cell neoplasm	1
Benign disease	
Adenoma	2
Haemangioma	2
Focal nodular hyperplasia	3
Biliary cystadenoma	1
Extent of resection	
Right hepatectomy	15
Extended right hepatectomy (including segment IV)*	11
Right hepatectomy plus left wedge resection	5
Left hepatectomy	3

*Includes one patient who underwent complete resection of the caudate lobe

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planned limits of resection were first marked on Glisson's capsule using diathermy coagulation, and after vascular occlusion (see below) liver transection was performed by crushing the hepatic tissue with a pair of artery forceps. The delineated branches of the vascular and biliary system thus isolated were divided between metal clips or ligatures. At the end of the procedure the portal pedicle and hepatic vein were transected using a vascular stapling device. This intraparenchymal approach without prior ligation of the hilar vessels or hepatic veins was considered the safest procedure in relation to possible anatomical abnormalities. All 34 patients underwent major hepatectomy, i.e. resection of at least three segments according to Couinaud[12] (*Table 1*). At the end of the procedure, the hepatic fossa was drained with two large-bore silicone drains brought out through separate stab incisions in the right abdominal wall.

Vascular control. All 34 liver resections were performed with temporary vascular occlusion to reduce intraoperative bleeding. Occlusion was applied continuously without intermittent release of the vascular clamps. Liver cooling such as topical refrigeration or hypothermic perfusion was not used. Vascular occlusion was performed by continuous portal triad clamping, the Pringle manoeuvre[13], in 15 patients. In a further 15 patients hepatic vascular exclusion, i.e. portal triad clamping as well as occlusion of the inferior vena cava below and above the liver[5,14], was performed during resection. The exclusion technique was indicated for resection of large hypervascular or posterior tumours located close to the vena cava or hepatic veins, which carry a high risk of haemorrhage or air embolism during hepatectomy. In four patients both manoeuvres were performed sequentially; in two clamping of the inferior vena cava in addition to portal triad clamping was necessary because of uncontrolled bleeding from a hepatic vein during liver transection. Two other patients in whom major resection was performed using hepatic vascular exclusion subsequently underwent a further non-anatomical resection from the liver remnant using portal triad clamping alone after release of the caval clamps.

Intraoperative temperature control

Throughout the study period, warming therapy was applied to minimize intraoperative hypothermia. Measures used included body insulation, inspiratory gas and liquid replacement heating, a circulating water mattress and, since 1987, leg warming by a heating blanket. Intraoperative core temperature was measured using a thermistor placed in a Swan–Ganz catheter.

Postoperative management

After operation patients were transferred to the intensive care unit. They had daily clinical examinations, including screening for evidence of encephalopathy. A coagulation profile was performed on the evening of operation and full blood chemistry daily during the first week and then twice weekly until discharge from hospital.

Antibiotic prophylaxis consisted of administration of a β-lactam drug for 48–72 h in association with an aminoglycoside and metronidazole. No anticoagulant therapy was used in the immediate postoperative period.

Statistical analysis

Deaths that occurred within 30 days of hepatectomy, and those during the initial hospitalization for liver resection, were included in the operative mortality data. The length of stay in the intensive care unit and in hospital after operation was recorded.

Several factors were analysed to determine their correlation with the postoperative course: weight of resected specimen, type of vascular occlusion, amount of blood transfused during surgery, duration of liver ischaemia and intraoperative core temperature.

Results are expressed as mean(s.e.m.). Differences between groups were tested with analysis of variance and Fisher's test for least significant difference. The χ^2 test, with Yates' correction when appropriate, was used to determine the significance of differences in the frequency of variables between groups. Correlation was evaluated by standard linear regression. Statistical analysis was carried out using a standard biomedical program (Statview II; Abacus Concepts, Berkeley, California, USA). $P < 0{\cdot}05$ was considered significant.

Results

Operative mortality

There were no intraoperative or postoperative deaths.

Postoperative morbidity

In 18 of the 34 patients the postoperative course was either uneventful or marked by asymptomatic mild pleural effusion (eight patients). Three patients required reoperation for postoperative bleeding following left hepatectomy (one patient), right hepatectomy (one) and extended right hepatectomy with partial resection of segments II and III (one). The duration of liver ischaemia for these patients was 60, 70 and 127 min respectively. The last patient had to undergo surgery again on the 15th day after operation for a bile leak. Four patients suffered transient liver failure with mild encephalopathy and ascites following right (two patients) and extended right (two) hepatectomy performed with vascular occlusion lasting for 70, 80, 85 and 90 min. The ascites resolved spontaneously within 15 days in all four cases. Other complications included pulmonary embolism (two patients), pneumonia or atelectasis (seven), wound infection (two) and cardiac arrhythmia (one). The mean(s.e.m.) lengths of stay in the intensive care unit and in hospital were 6·4(0·9) (range 1–25) and 17·6(1·5) (range 7–42) days respectively. The incidence of postoperative complications correlated significantly with stay in intensive care ($F = 10{\cdot}04$, $P = 0{\cdot}003$) and in hospital ($F = 19{\cdot}93$, $P = 0{\cdot}0001$).

Intraoperative management

The mean(s.e.m.) duration of continuous vascular occlusion and of the surgical procedure was 73·6(2·5) and 390(140) min. In one case, vascular occlusion was extended to 127 min because of a technically difficult hepatectomy. The mean(s.e.m.) core temperature during liver ischaemia was 35·0(0·2) (range 32·7–37·4)°C. It was 35·1(0·3) (range 32·1–37·1)°C at the end of the procedure after the abdomen had been closed and the patient transferred to the recovery room. The mean(s.e.m.) intraoperative blood transfusion was 5·3(0·8) (range 0–19) units packed red cells. For the last 23 patients in the series, operated on between 1987 and 1991, the amount of blood transfused had reduced to a mean(s.e.m.) of 2·6(1·8) (range 0–6) units. Six patients were not transfused. *Table 2* summarizes the relationships between the duration of liver ischaemia and parameters observed during and after resection. The amount of blood transfused and the length of stay in intensive care correlated positively with the duration of liver ischaemia. Monitoring of expired carbon dioxide and pulmonary artery pressure revealed no evidence of air embolism.

Liver function

Postoperative changes in the levels of serum transaminases, bilirubin and in coagulation are shown in *Table 3*. There was a 13-fold rise in transaminase levels on day 1. By day 7 ALT and AST levels had fallen to fivefold and twofold of their preoperative value. No correlation was found between the level of transaminases on day 1 and the duration of liver ischaemia (*Table 2*). There was a fall in prothrombin and proaccelerin levels on day 1 to 48 and 45 per cent of normal values respectively. These values were >60 per cent of normal by day 3 in 25 patients. The proaccelerin level on day 1 did not correlate with the duration of liver ischaemia (*Table 2*).

Table 2 *Relationship between duration of continuous normothermic liver ischaemia and parameters observed during and after major hepatectomy*

	Mean(s.e.m.)	*r*	*P*
Weight of specimen (g)	1010(94)	0·20	0·26
Core temperature during ischaemia (°C)	35·0(0·2)	0·08	0·70
Blood transfused (units packed red cells)	5·3(0·8)	0·45	0·008
Serum levels on day 1			
Aspartate transaminase (units/l)	390(50)	0·01	0·95
Alanine transaminase (units/l)	437(78)	0·14	0·53
Proaccelerin (%)	45(2)	0·12	0·52
Length of stay (days)			
Intensive care	6·4(0·9)	0·36	0·04
Hospital	17·6(1·5)	0·22	0·21

Table 3 *Changes in the levels of serum liver enzymes following major hepatectomy with continuous normothermic ischaemia for >60 min*

	Before surgery	After operation		
		Day 1	Day 3	Day 7
Aspartate transaminase (units/l)	18(2)	390(50)	185(78)	40(3)
Alanine transaminase (units/l)	21(2)	437(78)	284(102)	100(22)
Bilirubin (μmol/l)	12(1)	91(17)	92(19)	59(12)
Prothrombin (%)	94(2)	48(3)	67(3)	77(3)
Proaccelerin (%)	98(1)	45(2)	64(3)	85(3)

Values are mean(s.e.m.)

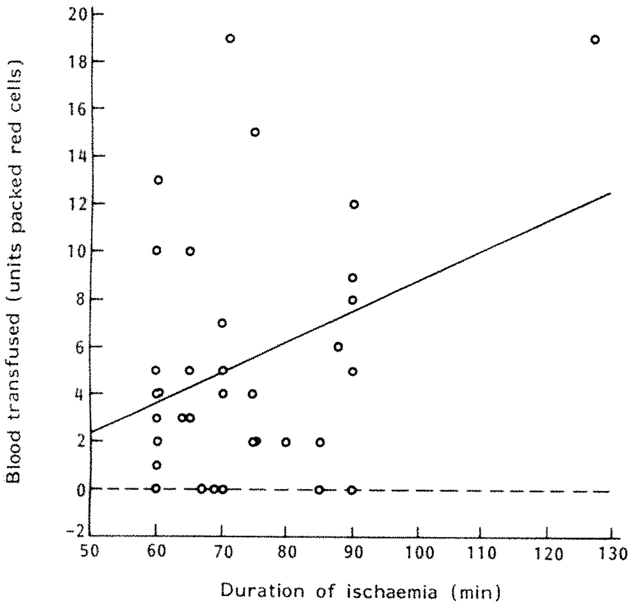

Figure 1 *Relationship between the duration of liver ischaemia and the amount of blood transfused.* r = *0·45*, P = *0·008*

Factors affecting morbidity

Amount of blood transfused. Although the amount of blood transfused during surgery correlated with the length of stay in the intensive care unit ($r = 0{\cdot}52$, $P = 0{\cdot}002$) and in hospital ($r = 0{\cdot}51$, $P = 0{\cdot}002$), the relationship between transfusion and the incidence of postoperative complications was not significant ($F = 1{\cdot}48$, $P = 0{\cdot}2$).

Weight of resected specimen. For all 34 patients, the mean(s.e.m.) weight of the resected specimen was 1010(94) g. The lengths of intensive care and hospital stay were related to the weight of the liver specimen ($r = 0{\cdot}46$, $P = 0{\cdot}006$; $r = 0{\cdot}47$, $P = 0{\cdot}005$ respectively). There was a significant correlation between the weight of the resected specimen and the occurrence of postoperative complications ($F = 4{\cdot}9$, $P = 0{\cdot}03$), but no relationship was found between the weight of the specimen and intraoperative blood loss.

Duration of liver ischaemia. There was no correlation between the duration of hepatic ischaemia and the occurrence of postoperative liver failure ($F = 1{\cdot}3$, $P = 0{\cdot}26$) or complications ($F = 0{\cdot}001$, $P = 0{\cdot}98$). The duration of ischaemia correlated with the amount of blood transfused ($r = 0{\cdot}45$, $P = 0{\cdot}008$) (*Figure 1*) and the length of stay in intensive care ($r = 0{\cdot}36$, $P = 0{\cdot}04$) (*Figure 2*) but not with the duration of stay in hospital (*Table 2*). Two groups of patients were compared: those in whom the duration of liver ischaemia was <75 min (mean(s.e.m.) 64·3(1·0) (range 60–74) min; $n = 20$) and those in whom the duration was ⩾75 min (mean(s.e.m.) 86·8(3·5) (range 75–127) min; $n = 14$) (*Table 4*). No difference was noted between the two groups with regard to the incidence of liver failure, postoperative complications, the amount of blood transfused, or length of stay in the intensive care unit or hospital.

Type of vascular control. When comparing patients undergoing liver resection with portal triad clamping alone (15) with those operated on with hepatic vascular exclusion alone (15), no significant difference in the postoperative course was found (*Table 5*). The only significant difference in intraoperative measurements was a lower mean core temperature during ischaemia in patients undergoing vascular exclusion.

Core temperature during liver ischaemia

Patients in whom the core temperature during vascular occlusion was <35°C (mean(s.e.m.) 34·1(0·2)°C; $n = 17$) were compared with those in whom it was ⩾35°C (mean(s.e.m.) 36·0(0·2)°C; $n = 17$). No significant difference was noted between the groups regarding the extent of hepatectomy, weight of the resected specimen ($P = 0{\cdot}10$) or the duration of vascular occlusion ($P = 0{\cdot}42$). Postoperative biochemical changes in patients with mean core temperature <35°C or ⩾35°C were not significantly different on day 1 (mean(s.e.m.) AST 389(63) and 424(79) units/l, $P = 0{\cdot}36$; ALT 387(41) and 511(141) units/l, $P = 0{\cdot}22$; proaccelerin 45(3) and 45(4) per cent,

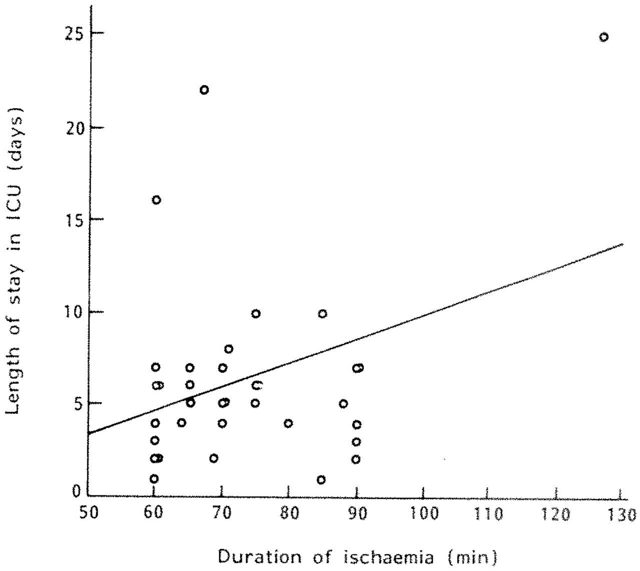

Figure 2 *Relationship between the duration of liver ischaemia and the length of stay in the intensive care unit (ICU).* r = *0·36*, P = *0·04*

Table 4 *Influence of the duration of normothermic liver ischaemia in 34 patients undergoing major hepatectomy with continuous vascular occlusion for >60 min*

	Ischaemia <75 min ($n = 20$)	Ischaemia ⩾75 min ($n = 14$)
Duration of ischaemia (min)*	64·3(1·0)	86·8(3·5)
Weight of specimen (g)*	989(88)	1039(194)
Blood transfused (units packed red cells)*	5·1(1·2)	7·0(1·8)
No. of patients with complications	10	6
No. with transient liver failure	1	3
Length of stay (days)*		
Intensive care	6·1(1·1)	6·8(1·6)
Hospital	17·1(1·9)	18·5(2·5)

*Values are mean(s.e.m.)

Table 5 *Influence of the type of vascular occlusion in 30 patients undergoing major hepatectomy*

	Portal triad clamping ($n = 15$)	Hepatic vascular exclusion ($n = 15$)
Weight of specimen (g)*	809(73)	1095(162)
Duration of ischaemia (min)*	70(3)	72(3)
Core temperature during ischaemia (°C)*	35·6(0·3)	34·6(0·3)†
Blood transfused (units packed red cells)*	5·0(1·4)	5·8(1·2)
No. of patients with complications	4	8
No. with transient liver failure	1	1
Length of stay (days)*		
Intensive care	4·7(1·0)	5·6(0·5)
Hospital	14·7(1·4)	17·8(2·5)

*Values are mean(s.e.m.). †P = 0·03

P = 0·48, respectively). The mean(s.e.m.) amount of blood transfused during operation was greater in patients with core temperature <35°C (6·6(1·3) units packed red cells) than in those with a core temperature $\geqslant 35$°C (3·5(0·9) units) (P = 0·03).

Discussion

More than 80 years after the first report of portal triad clamping by Pringle[13] in 1908, temporary occlusion of the blood supply to the liver is widely accepted as an efficient manoeuvre to decrease bleeding during liver surgery. Moreover, it has been shown that intraoperative bleeding is a major prognostic factor[1–3] and that the use of vascular clamping reduces the amount of blood transfused during liver resection[2].

Although the maximal advisable duration of normothermic liver ischaemia has dramatically increased in recent years, the upper limit remains unknown. The fear of adverse effects associated with prolonged warm liver ischaemia and the need for longer periods of vascular clamping have led to the revival of surgical procedures such as *in situ*[15] or *ex situ*[16,17] hypothermic hepatic perfusion. These approaches, introduced by Fortner *et al.*[15], have been used when a technically challenging hepatectomy was foreseen. With the use of hypothermic perfusion, major liver resection (often including vascular reconstruction) has been performed with periods of vascular occlusion[15–17] extending up to 9 h. The question remains whether hypothermic perfusion has any benefit for shorter periods of vascular occlusion, i.e. when clamping for >60 min is expected.

Since the beginning of the 1980s a policy of continuous vascular occlusion during liver surgery, mainly through the development of hepatic vascular exclusion, has been adopted in the authors' department. In the present series of 34 major liver resections with a single period of vascular occlusion >60 min, hospital mortality was nil and the postoperative course was uneventful in >50 per cent of patients. For the larger and more complex resections, the mean amount of blood transfused during operation was only 5·3 units packed red cells. Improvements in surgical technique and meticulous attention to haemostasis reduced the mean transfusion rate to 2·6 units packed cells per patient during the last 5 years of the study period, including six patients who underwent major liver resection without blood transfusion. Despite this reduction in blood requirement, there is still a correlation between intraoperative blood transfusion and the length of intensive care and hospital stay, confirming the importance of transfusion in the postoperative course in liver surgery.

The present study confirms the tolerance of liver cells to prolonged normothermic ischaemia. Liver failure was rarely encountered and was always mild and transient. Furthermore, neither the incidence of liver failure nor the occurrence of postoperative complications was related to the duration of hepatic ischaemia. Changes in serum liver enzyme levels were always transient with a trend returning towards the preoperative level within the first week. Unlike other reports[7], but in agreement with the authors' previous results[1] and those of Huguet *et al.*[10], no correlation was found between postoperative transaminase levels and the duration of ischaemia. Indeed, liver ischaemia is not the only factor responsible for release of transaminases. Surgical trauma probably contributes considerably to this, as suggested by the eightfold increase in serum levels of transaminases seen after hepatectomy performed with no vascular occlusion[3]. Again, the serum level of proaccelerin on day 1 did not correlate with the duration of ischaemia, whereas it was significantly related to the weight of the resected specimen. Thus, the biochemical changes after liver resection with prolonged normothermic ischaemia appear impressive but transient.

It has been advocated[5] that moderate hypothermia during liver resection might improve the tolerance of liver cells to prolonged ischaemia. The present results do not support this hypothesis: the postoperative changes in biochemical liver test results were similar in patients regardless of the core temperature during ischaemia. As intraoperative hypothermia has many documented deleterious effects[18], particularly on haemostasis and blood loss, it seems preferable to use various warming devices to minimize the fall in core temperature during major hepatectomy.

Long-term ischaemia has also been reported[8] with the use of intermittent portal triad clamping for cycles of vascular occlusion of 20 min each, followed by reperfusion of the liver for 5 min. This allows a long duration of liver ischaemia, ranging up to 150 min, with low mortality and morbidity and transient changes in serum liver enzyme levels[8]. However, the authors have used continuous vascular occlusion to perform major liver resection in safe, stable haemodynamic conditions[19] with minimal blood loss. The main advantage of continuous clamping of the porta hepatis is to avoid the bleeding that inevitably occurs during periods of clamp release. Haemorrhagic and hypotensive episodes are more likely to occur following release of the vascular clamps, leading to increased haemodynamic disturbance during the subsequent periods of clamping. Intraoperative hypotension has been associated with an increased risk of recurrence after liver resection for colorectal metastases[20]. Continuous clamping should theoretically reduce operative bleeding and the duration of the surgical procedure. Lastly, intermittent vascular occlusion is not appropriate when the characteristics of the tumour indicate hepatic vascular exclusion. The major point that remains to be determined is whether rewarming of the liver parenchyma during sequential reperfusion cycles contributes to a less favourable tolerance to prolonged ischaemia compared with straightforward clamping.

The authors' current policy is to use continuous vascular occlusion, which enables safe, haemodynamically stable and bloodless liver resection to be performed. Whenever the foreseen complexity of the hepatectomy suggests that vascular occlusion might exceed 120 min, we strongly advocate hepatic vascular exclusion with *in situ* hypothermic perfusion of University of Wisconsin preserving solution[21].

In conclusion, prolonged continuous vascular occlusion appears to be a safe, useful and non-deleterious manoeuvre for major liver resection. Continuous clamping may be applied for up to 90 min in healthy parenchyma.

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Computed tomography and fine-needle aspiration cytology for preoperative evaluation of cystic tumours of the pancreas

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Cystic neoplasms of the pancreas are rare. They may present as a mucinous (malignant or potentially malignant) tumour or as benign serous cystadenoma. Accurate preoperative diagnosis is therefore essential, as an asymptomatic serous tumour may safely be followed clinically for years, whereas mucinous tumours require aggressive surgery. Thirteen patients with cystadenoma and cystadenocarcinoma of the pancreas were reviewed and how best to improve the rate of preoperative diagnosis was considered. Fine-needle aspiration cytology and computed tomography enable accurate preoperative distinction between mucinous and serous cystic tumours of the pancreas.

Cystadenoma and cystadenocarcinoma of the pancreas account for only 1 per cent of pancreatic neoplasms[1]. Since these tumours are rare, they may be mistaken for pseudocysts. Inadequate or inappropriate treatment, such as cystenterostomy of cystadenocarcinoma, may then be performed[2]. This is unfortunate because cystadenocarcinoma may be cured surgically. The prognosis of such malignant cysts is more favourable than that of the more common solid adenocarcinoma of the pancreas: after total excision, non-metastatic cystadenocarcinoma carries a 10-year survival rate of 70 per cent[3] compared with 30 per cent at 2 years for solid adenocarcinoma[4]. Accurate preoperative diagnosis is therefore essential to allow the correct choice of operative procedure and to enable appropriate treatment of neoplastic pancreatic cysts.

Cystic pancreatic tumours are either serous or mucinous. It is essential to differentiate between these two subtypes, as the former is usually benign whereas the latter is malignant or potentially so[5]. Computed tomography (CT) remains the first-choice diagnostic tool[6]. Percutaneous fine-needle aspiration cytology (FNAC) has recently been used in the diagnosis of these tumours[6], although its role is still under evaluation. The purpose of the present study was to review a series of cystic pancreatic tumours from this institute and other reported results to select CT and FNAC criteria that may lead to more accurate preoperative diagnosis.

Patients and methods

The records of 13 patients who were diagnosed as having a cystic neoplasm of the pancreas were reviewed. Five further patients were diagnosed at autopsy: one 90-year-old woman who died shortly after admission with abdominal distension had metastatic mucinous cystadenocarcinoma of the pancreas and four patients had an incidental cystadenoma diagnosed after death from an unrelated cause.

When the histological diagnosis appeared uncertain, the slides were re-examined by a pathologist. Clinical follow-up was obtained through the patient's personal physician or at outpatient attendance.

Nine of the ten original CT films were available; these were reinterpreted according to accepted radiological criteria[7] by a radiologist unaware of the clinical and histological findings. The radiologist recorded cyst number and size, and the presence of a central scar and malignant invasion. Four patients underwent preoperative FNAC; the aspirates were examined for cytological characteristics, and content of extracellular and intracellular mucin, and intracellular glycogen.

Results

The 13 patients comprised 11 women and two men of mean age 52 years. Four patients had histologically proven mucinous cystadenoma, five mucinous cystadenocarcinoma and four a serous tumour. Details are given in *Table 1*.

Eight patients had symptoms related to the cystic tumour: seven complained chiefly of abdominal pain, five had weight loss and two showed worsening of diabetes. Two further patients had diarrhoea and one suffered from major haematemesis. The tumour was discovered fortuitously in two patients. On physical examination, five patients had a palpable mass. Jaundice was not encountered. The mean tumour diameter was 10 (range 3–18) cm. There was no difference in tumour location between the pancreatic head or tail (*Table 1*).

Abdominal CT and ultrasonography were the main investigations used, except for the first three patients because these techniques were not available at that time. The surgeon was aware of the diagnosis before operation in six of 12 cases (one patient did not undergo surgery). When the nine CT images were reinterpreted, serous and mucinous tumours were correctly identified in six patients (*Table 2*). FNAC was used in four tumours and diagnosed one serous and one mucinous cystadenoma, but was inconclusive in the other two cases (*Table 3*).

Ten partial pancreatic resections were performed: three pancreatoduodenectomies and seven left splenopancreatectomies (*Table 1*). Total pancreatectomy was necessary in three cases: two tumours invaded the whole gland and one pancreatoduodenectomy specimen showed diffuse mucinous dysplasia on peroperative frozen-section histology. An asymptomatic 78-year-old woman (patient 5) did not undergo operation. Subsequent FNAC supported this course of action, as it showed a serous cystadenoma. This patient remains free from symptoms.

Only one patient of the 12 who left hospital developed recurrent disease. This patient remains alive following repeat surgery (*Table 1*).

Discussion

Cystic pancreatic tumours occur predominantly in women[3,8–12]; in the present series, 11 of 13 patients were female. Nine tumours were mucinous, five of these malignant. Clinical symptoms were not characteristic, although some could be related to pancreatic dysfunction in half of the cases, such as worsening of diabetes, diarrhoea and weight loss. There was only one local recurrence, which confirmed that localized cystic pancreatic tumours are

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Table 1 *Details of 13 patients with cystic neoplasms of the pancreas*

Patient no.	Sex	Age (years)	Related symptoms	Tumour		Surgery	Histopathology	Outcome
				Site	Size (cm)			
1	F	50	No	Tail	Diameter 16–18	Left splenopancreatectomy	Mucinous cystadenocarcinoma	No recurrence for 22 years; lost to follow-up 6 years ago
2	F	53	Yes	Tail	Diameter 15	Left splenopancreatectomy and segmental transverse colectomy	Mucinous cystadenoma	Well after 30 years
3	F	46	Yes	Tail	7 × 6 × 6	Left splenopancreatectomy	Mucinous cystadenoma	Well after 19 years
4	F	41	Yes	Head, body and tail	8 × 7 × 3	Left splenopancreatectomy and subsequent subtotal pancreatectomy	Mucinous cystadenocarcinoma	Well after 14 years
5	F	78	No	Head	Diameter 12	None	Serous cystadenoma	Well after 14 years
6	M	68	Yes	Head and body	10 × 7 × 8	Pancreatoduodenectomy	Mucinous cystadenocarcinoma	Recurrence after 9 years in the pancreatic bed and left liver; total pancreatectomy, left hepatectomy. Well after 18 months' follow-up
7	F	76	Yes	Head	Diameter 8	Pancreatoduodenectomy	Serous cystadenoma	Died 3 weeks after operation from septic complications
8	F	25	Yes	Body and tail	12 × 11 × 6	Left splenopancreatectomy	Mucinous cystadenoma	Well after 3 years then lost to follow-up
9	F	62	No	Head and body	Diameter 12	Pancreatoduodenectomy	Serous cystadenoma	Well after 8 years
10	F	36	Yes	Tail	Diameter 6	Left splenopancreatectomy	Serous cystadenoma	Well after 7 years
11	F	45	Yes	Head, body and tail	12 × 6 × 3·5	Total splenopancreatectomy	Mucinous cystadenocarcinoma	Well after 5 years
12	M	67	No	Head	7 × 6 × 3	Total splenopancreatectomy	Mucinous cystadenocarcinoma	Well after 1·5 years
13	F	28	No	Tail	Diameter 15	Left splenopancreatectomy	Mucinous cystadenoma	Well after 7 months

Table 2 *Reinterpretation of computed tomography data for presence of diagnostic criteria*

Patient no.*	Cyst diameter (cm)		Cyst number		Central scar present	Prediction
	≤2	>2	≤6	>6		
4	+		+			Inconclusive
5	+			+	+	Correct
6	+			+		Wrong
7	+			+	+	Correct
8		+	+			Correct
9	+			+	+	Correct
10		+	+			Wrong
11		+	+			Correct
13		+	+			Correct

*The first three patients were treated before computed tomography was available

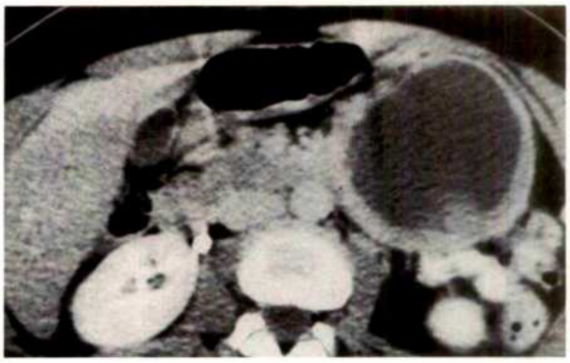

Figure 1 *Mucinous cystadenoma of the tail of the pancreas. The single cyst is large and has a relatively thick wall; there is a papillary proliferation on the inner posterior border. Note that there is no local invasion*

curable provided that there is no malignant dissemination at operation[10]. The absence of metastases at presentation explains the present high survival rate (92 per cent after median follow-up of 8 years), which is slightly higher than usually reported[3,6,8,9,11,13].

The present low rate of correct diagnosis before operation, which is shared by others[2], led to the review of preoperative investigation of these patients. All authors agree that CT is the most important initial procedure[6,7,14,15]. It indicates the size and number of cysts, which are cardinal parameters: mucinous tumours usually have a small number of large cysts whereas serous lesions typically have many small cysts. Johnson *et al.*[7] reviewed CT of 35 pancreatic cystic neoplasms and correctly distinguished mucinous from serous tumours in over 90 per cent of cases. Of the four criteria defined in that study, two were usually diagnostic. With a cyst diameter >2 cm and six or fewer cysts, a mucinous tumour is most probable (*Figure 1*). On the other hand, if the cyst diameter is ≤2 cm and there are more than six of them, a serous tumour is highly likely (*Figure 2*). These morphological features of serous adenoma correspond to the honeycomb or alveolar appearance on CT[11,16], which represents enhancement of the cyst walls after injection of intravenous contrast. The other parameters described by Johnson *et al.*[7] are of less importance: a central scar is suggestive of a serous tumour whereas local tumour invasion suggests cystadenocarcinoma.

Table 3 *Cytological appearance and diagnostic prediction from fine-needle aspiration cytology*

Patient no.	Malignant cytology	Mucin coloration	Glycogen coloration	Amylase level (units l^{-1})	Prediction
5	No	No	Yes	Not measured	Correct
6	No	Not performed	Not performed	Not measured	Inconclusive
8	No	Not performed	Not performed	75000	Inconclusive
13	No	Yes	No	Not measured	Correct

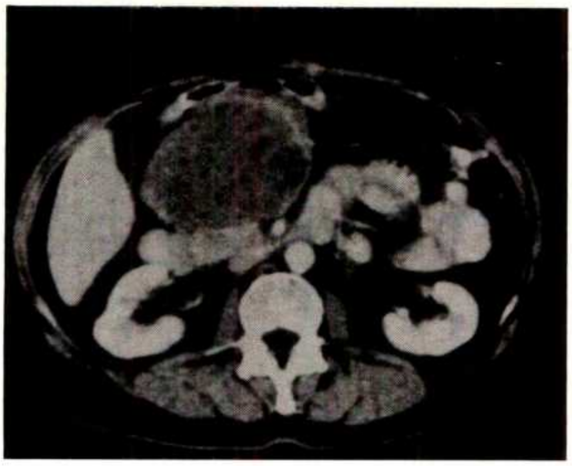

Figure 2 *Serous cystadenoma of the head of the pancreas. The typical honeycomb appearance of these numerous microcysts is best seen after contrast enhancement and with thin (<5 mm) slices*

When the present CT images were reinterpreted according to these criteria, the results were less successful than those of Johnson *et al.*[7], with correct identification in only two-thirds of the present cases (*Table 2*). The experience with preoperative FNAC was therefore re-examined to assess the additional contribution this technique could offer.

FNAC was rarely performed in this institute before 1987. Since then it has been observed that mucin is a reliable cytological feature of mucinous pancreatic tumours[12,17–24]. The diagnosis was made in this way in patient 13 (*Table 3*). Detection of mucin is technically simple and may be performed during operation[6]. Serous tumours can be reliably identified by high intracellular content of glycogen[19,23–25].

All the present FNAC specimens were examined using conventional cytology. The false-negative result in patient 6 could be caused by the characteristically scattered distribution of malignancy in pancreatic cystadenocarcinoma. Two other groups[26,27] claimed a comparable accuracy of cytology with two-thirds of diagnoses confirmed (six of nine patients). Conventional cytology is also useful to exclude the diagnosis of inflammatory pseudocyst, which has no epithelial cells[18,27].

Carcinoembryonic antigen in cyst fluid was not assayed in the present study, although some authors have found high levels in cystadenocarcinoma[17,21,27–29]. This technique may be useful when cystadenocarcinoma is suspected.

FNAC appears to be valuable in preoperative diagnosis but there are two problems with this technique. First, the aspirated material is not always sufficient to allow diagnosis[28,29]; nevertheless, the specificity is 100 per cent and the sensitivity 80 per cent. Second, some cases of needle-track seeding have been reported, a complication that usually occurs after biopsy performed with large-bore needles[30].

The criteria that enable distinction between mucinous and serous tumours are summarized in *Figure 3*. The presence or absence of mucin is a cardinal feature that is usually diagnostic if other criteria are difficult to interpret.

If the tumour is mucinous, radical surgery is the only curative solution. There may be a contraindication to surgery in some cases, such as involvement of major vessels, and palliative internal drainage may be indicated for digestive tract obstruction or obstructive jaundice.

If the tumour is serous, and therefore not life-threatening, the type of surgery depends on the patient's general condition. If there is no contraindication to general anaesthesia any serous tumour should be resected as this leaves no doubt about the final diagnosis. In a patient with relative contraindications to anaesthesia only symptomatic tumours should be operated on[31]. Those located in the body and tail may usually be completely resected as left pancreatectomy is a well tolerated procedure. By contrast, there is no indication for radical resection of cystadenoma in the pancreatic head of a high-risk patient as the operative morbidity rate accompanying pancreatoduodenectomy is high. In such cases, the authors now favour palliative internal drainage. This approach might have been better for patient 7, who died from septic complications after pancreatoduodenectomy (*Table 1*). The recent report of a unique case of malignant serous cystadenocarcinoma[32] emphasizes, however, that non-operated serous cystadenoma requires regular follow-up.

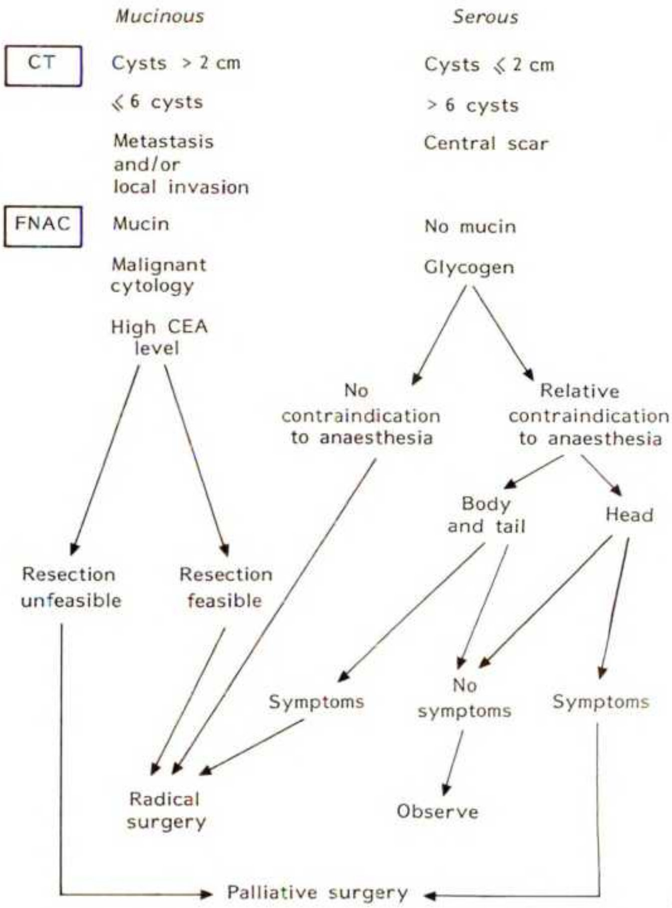

Figure 3 *Preoperative diagnosis and treatment of cystic tumours of the pancreas. FNAC, fine-needle aspiration cytology; CEA, carcinoembryonic antigen*

In conclusion, CT and FNAC used together enable a preoperative diagnosis in most cystic tumours of the pancreas. This may lead to better operative strategy, and may also spare an elderly asymptomatic patient with a serous tumour from a high-risk laparotomy.

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Morphological studies of graft pancreatitis following pancreas transplantation

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Morphological findings in the initial stages of graft pancreatitis were studied systematically in sequential biopsies of 16 human pancreatic allografts. In 14 patients clinical and morphological signs of graft pancreatitis developed in the early postoperative period. In all cases disturbances in the integrity of structures within acinar cells occurred during ischaemia. In ten cases activation of autophagocytosis occurred following reperfusion, with acceleration of cellular metabolism. After reperfusion a marked leucocyte reaction occurred with a later single acinar cell necrosis in six cases. At the same time, high serum pancreatic enzyme concentrations were observed in all patients following transplantation. Exocrine secretion from the allografts via the pancreatic duct was reduced, correlating with the severity of graft pancreatitis. Studies in this clinical situation might complement analyses of the cascade of morphological and pathophysiological reactions during the early stages of other types of acute pancreatitis.

Few factors involved in the pathogenesis of acute pancreatitis have been defined. It is assumed that uniform cascade-like premature activation of pancreatic proenzymes causes autodigestion of the gland[1–4]. It has been impossible to obtain human pancreatic tissue during the initial stages of the disease, and knowledge of the initial morphological and biochemical changes is based almost exclusively on animal studies. It is difficult to extrapolate these results to the clinical situation[5,6].

Following pancreas transplantation a clinical picture corresponding to acute pancreatitis may develop (graft pancreatitis) and this is ascribed to damage caused by ischaemia and/or preservation of the organ[7–10]. Prospective studies are possible from the onset of graft pancreatitis.

The pathophysiology and morphological changes in the exocrine parenchyma of human pancreas transplants were examined with emphasis on the initial morphological alterations in the biopsy material.

Patients and methods

Thirty-nine combined pancreas–kidney transplantations were performed between January 1987 and November 1990. All patients had diabetes mellitus type I and end-stage renal disease. Most showed further severe secondary diabetic complications.

Removal of the organs from the donors was carried out under stable circulatory conditions. *In situ* perfusion was performed initially with Eurocollins solution, but since August 1988 with University of Wisconsin solution, using a solution kept at 4°C and a balloon catheter in the aorta. Further surface cooling of the pancreas was carried out with iced water. The complete pancreas was removed with the spleen, duodenum and vessels of supply. The organs were continuously cooled at 4°C until reperfusion.

Following prospective negative T cell cross-matches, favourable correspondence of the human leucocyte antigen (HLA) system was used to help select recipients. An incomplete HLA match was not considered a contraindication to transplantation. The whole pancreas with a segment of duodenum was transplanted using the bladder drainage technique[11,12] described by Corry. A side-to-side anastomosis between the duodenal segment and the urinary bladder allowed pancreatic juice to drain into the bladder for excretion in the urine. Three drains were placed next to the pancreas allograft and in the pouch of Douglas, and closed continuous peritoneal lavage carried out with modified peritoneal dialysis solutions (PD11, PD14; Schiwa, Glandorf, Germany) starting 6–12 h after operation. Lavage was performed using mechanical control (APD06; Dialyse Technik, Rheinstetten-Forchheim, Germany) to regulate the volume and frequency (300–500 ml per cycle, 10–15 litres per day). The amylase and lipase content and leucocyte count of the lavage fluid were measured.

Immunosuppressive therapy was started during operation with prednisolone 500 mg and azathioprine 2–3 mg kg^{-1} day^{-1}. After the first postoperative day, cyclosporin A was added to maintain a blood level of 250–300 ng dl^{-1}. In addition, antithymocyte globulin 0·15 ml kg^{-1} day^{-1} was given prophylactically for 10 days. To avoid graft thrombosis, low molecular weight dextran (Thomadex; Thomae, Biberach/Riss, Germany), 250 ml per day for 5 days, and heparin were given intravenously. The heparin dose was adjusted according to the prothrombin time, aiming at a value of 50–60 s during the first 10 days. Later, aspirin, 250 mg per 48 h, was given for long-term anticoagulation. Blood cell count and levels of serum transaminases, amylase, lipase, creatinine and electrolytes, and urine electrolytes and amylase were determined, depending on the clinical situation.

Morphological examination

To assess initial morphological changes, 16 pancreatic grafts transplanted between December 1988 and November 1990 were subjected to serial perioperative biopsy. Tissue samples, measuring approximately 5 × 5 × 5 mm, were taken from the tail of the pancreas immediately before and after cold ischaemia and at 30 min, 90 min and 5–6 h after reperfusion of the graft. Additional specimens were obtained during any reoperations required between 7 and 20 days after transplantation. On removal, tissue samples were immediately fixed in phosphate-buffered 3 per cent glutaraldehyde. The material was further fixed with osmium tetroxide, contrasted *en bloc* in uranyl acetate and embedded in Epon 812 (Fluka, Buchs, Switzerland) for light and transmission electron microscopy. For the purpose of preliminary orientation and light microscopy findings, semithin sections (1·0–1·5 μm) were prepared and stained with methylene blue and basic fuchsine. Ultrathin sections (0·08–0·15 μm) were contrasted in uranyl acetate and lead citrate and examined with a transmission electron microscope (EM 10; Zeiss, Oberkochen, Germany).

Diagnosis of graft pancreatitis

The diagnosis of graft pancreatitis was made following evaluation of clinical symptoms, laboratory findings, the results of ultrasonography and computed tomography, and macroscopic appearance at reoperation.

Results

Organ preservation and duration of graft ischaemia

Eurocollins solution was used in 14 pancreatic–renal transplants for organ preservation. The mean duration of ischaemia was 4 h 50 min (range 2 h 45 min to 6 h 20 min) for

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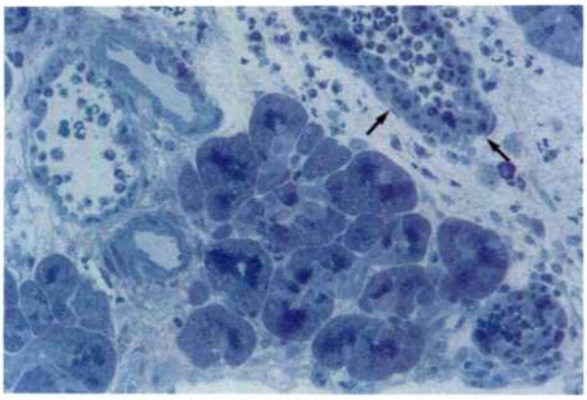

Figure 1 *Leucocyte migration (arrows) between endothelial cells and into the perivascular tissue 90 min after reperfusion. Uneven distribution of zymogen granules within the acinar epithelial cells can be seen. (Basic fuchsine and methylene blue stain, original magnification × 480)*

pancreatic allografts and 7 h 30 min (range 5 h 30 min to 10 h 30 min) for renal allografts. After preservation with University of Wisconsin solution ($n = 25$), the mean duration of ischaemia was 8 h 45 min (range 5 h 30 min to 16 h 00 min) for pancreatic allografts and 12 h 10 min (range 8 h 00 min to 19 h 00 min) for renal allografts.

Initial graft function

Pancreas. In 36 of the 39 patients the initial endocrine function of the pancreas was adequate. Three patients required exogenous insulin for varying periods of time after operation owing to graft endocrine insufficiency.

Exocrine pancreatic function was evaluated on the basis of the amount of amylase secreted in the urine per 24 h. The mean amylase secretion was considerably reduced during the first days after operation (2500 units per 24 h on days 1–3). Until the 14th day there was a steady increase in urinary amylase levels from 4500 to 25 000 units per day. One patient suffered complete exocrine graft failure. After recovering exocrine graft function, most patients developed metabolic acidosis which required adjustment with oral or intravenous sodium bicarbonate.

Kidney. In 34 patients there was sufficient renal function to obviate the need for haemodialysis. The mean serum creatinine level decreased to 2·3 (range 0·9–6·5) mg dl^{-1} on day 7 and to 1·8 (range 0·9–4·5) mg dl^{-1} on day 14.

Serum amylase and lipase

All patients had increased serum amylase and lipase levels. The mean peak levels were detected during the first 36 h following reperfusion of the pancreatic allografts. The amylase level was increased 3–15-fold and that for lipase 4–30-fold. Within the first week about two-thirds of patients had normal serum pancreatic enzyme levels.

Graft pancreatitis

Graft pancreatitis developed in 14 patients. In eight patients oedematous pancreatitis was diagnosed; the other six patients underwent reoperation between days 7 and 20, and peripancreatic and intrapancreatic necrosis was verified by microscopy. Extensive debridement of the graft and surrounding tissue was performed in all patients. In two patients resection of the pancreatic tail was necessary.

Long-term function

No patient died as a result of graft pancreatitis. All patients except one need no exogenous insulin. The 1-year graft function rate for the series of 39 patients was 87 per cent for both organs.

Morphological findings

Macroscopic appearance. During reperfusion and removal of the organs, and at the end of the period of cold ischaemia, no pathological changes were detected macroscopically. In 12 grafts a distinct, predominantly subcapsular, oedema became evident about 2 h after reperfusion, but there were no signs of parenchymal necrosis. During the final evaluation, superficial white areas aligned along the subcapsular blood vessels were found in 15 allografts. Confluent (five cases) and non-confluent (ten) areas could be differentiated. Macroscopic signs of parenchymal haemorrhage were not seen.

Light and electron microscopy. Sixteen pancreatic allografts were biopsied after perfusion with University of Wisconsin solution.

Morphology subsequent to perfusion

Immediately after perfusion, light and electron microscopy detected no changes in the exocrine parenchyma of the pancreas.

Morphology before reperfusion

Light microscopic examination at the end of the period of cold ischaemia showed an unevenly distributed, slight oedema of the lobular septa and the interacinar connective tissue. Most of the acinar epithelial cells contained the typical number of zymogen granules in the apical parts of the cell. In single acinar epithelial cells the cytoplasm was loosened by oedema. The nuclei of these cells were displaced to the periphery of the cytoplasm. The centroacinar cells showed no alterations. The vascular lumen was mainly free from erythrocytes.

Electron microscopy of the material showed that the swelling of the acinar epithelial cells was due to pronounced changes in the endoplasmic reticulum. An increasing distension of the cisternae of the endoplasmic reticulum had developed, initially giving the impression of dilatation and partial vacuolization. The remaining organelles were in part displaced to the periphery of the cells, and the nuclei were indented. Small amounts of fine flaky material and individual osmiophilic membranes were seen in the distended spaces of the endoplasmic reticulum.

Morphology following reperfusion

Erythrocytes were regularly demonstrable in the capillary lumen 30 and 90 min after reperfusion. Between the endothelial cells of the blood vessels polymorphonuclear leucocytes were found infiltrating the vascular walls and subsequently the perivascular connective tissue (*Figure 1*). In single acinar cells, reduced numbers and irregular distribution of the zymogen granules was evident. Fusion figures were seen between zymogen granules and vacuoles of lesser electron density (*Figure 2*).

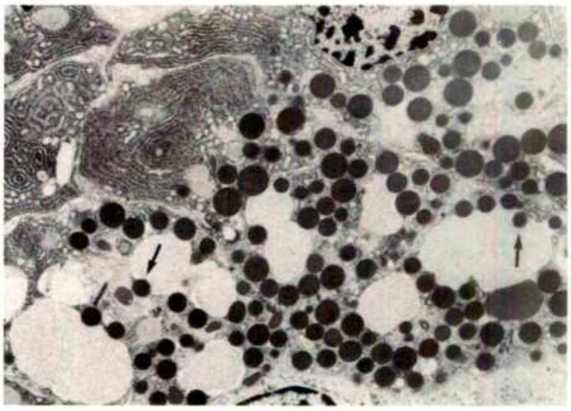

Figure 2 *Formation of vacuoles of different size within the acinar epithelial cells. Fusion (arrows) between zymogen granules and vacuoles of lesser electron density occurs 5 h after reperfusion. (Transmission electron microscopy, original magnification × 6700)*

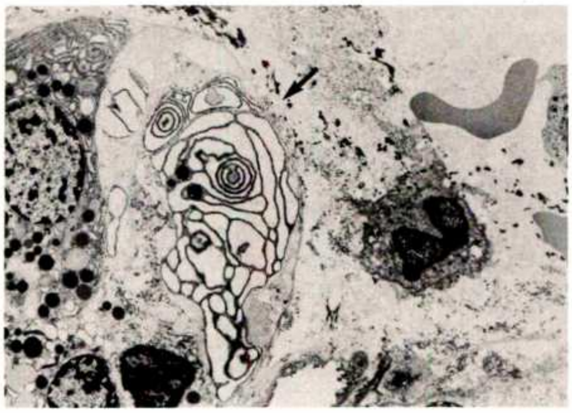

Figure 3 *Start of single cell necrosis (arrow) of acinar epithelial cells 6 h after reperfusion. There is destruction of cell membranes, involvement of capillaries, extravasation of erythrocytes, slight fibrin deposition and infiltration with granulocytes. (Transmission electron microscopy, original magnification × 4200)*

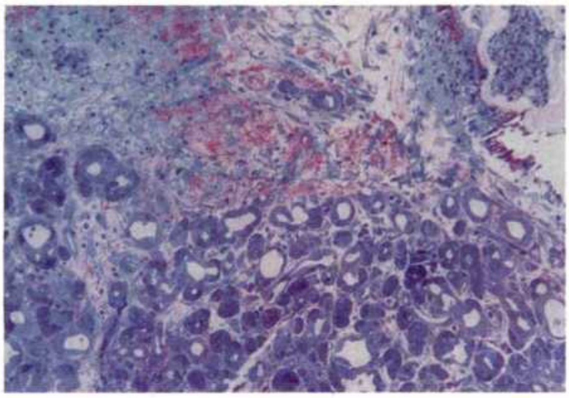

Figure 4 *Extensive necrosis of the exocrine pancreas with aggregation of macrophages at the edges. There is also distinct activation of local fibroblasts and neoformation of fibres. In areas of preserved parenchyma, exocrine activity is markedly reduced. (Basic fuchsine and methylene blue stain, original magnification × 260)*

Autophagolysosomes of varying size developed in the cytoplasm of the affected cells in ten cases. Their basic structure was in part characterized by membrane-like layered osmiophilic material and structures of different organelles. Granular particles were demonstrable with a homogeneous matrix similar to neutral lipids.

At 5–6 h after reperfusion, defects could be found in the plasma membrane of single acinar epithelial cells in six cases. Zymogen granules and part of the cytoplasm were liberated and entered the intercellular space. Haemorrhage, fibrin deposition and polymorphonuclear leucocyte infiltration of varying density occurred (*Figure 3*). The perivascular connective tissue was focally loosened by oedema and leucocyte infiltration.

In biopsies obtained during laparotomy, necrosis of the parenchyma and/or peripancreatic fatty tissue of varying intensity was demonstrated. In areas of intact exocrine pancreatic parenchyma the number of zymogen granules was markedly decreased, and in some cases patchy necrosis was seen with a marked increase in macrophage and fibroblast activity (*Figure 4*).

Discussion

The clinical results of pancreatic transplantation have improved since the introduction of the bladder drainage technique and new immunosuppressive strategies[13–15], and graft function rates after combined pancreatic–renal transplantation equal those after kidney transplantation alone[15–17].

Perioperative damage to the exocrine parenchyma is responsible for most of the early local and systemic complications of transplantation[7–9]. Considering the morphological findings and the typical blood and urine chemistry it is tempting to assume that ischaemia–reperfusion injury induces a form of acute graft pancreatitis. The morphological findings observed during reoperation in the present patients, and in previous biopsy and autopsy data, show inflammatory processes that correspond to the picture of autodigestive tryptic pancreatitis[18,19].

As in the acute pancreatitis induced by intravenous infusion of caerulein or choline-deficient and ethionine-supplemented diet, the initial stage of graft pancreatitis seems to be a disturbance of the 'secretory pathway'[19–25]. According to morphological criteria, normal enzyme synthesis, which probably depends on an intact energy metabolism, is altered. The strict compartmentalization necessary for acinar cell integrity (to prevent premature activation of proenzymes) is disturbed. Modifications of cellular integrity with imbalance of proteases and antiproteases caused by hypoxia can lead to activation of the lysosomal system, with crinophagy and acinar cellular necrosis[3,4,20–22,26].

The massive granulocyte infiltration found after reperfusion seems to be of special significance. Immunological factors do not play a major role, since such changes were not seen in isolated renal transplants[27]. Pancreas-specific leucotactic substances or oxygen free radicals could be responsible for this reaction. The pathophysiological consequences of this leucocyte infiltration are not fully understood but local and systemic reactions must be taken into consideration[28–30] as cascade-like activation of proenzymes via granulocyte hydrolases has been suggested[3,26].

The levels of pancreatic enzyme in serum and urine indicate that maximal damage and impairment of exocrine function develop during the first 3 days after transplantation. Following extreme parenchymal damage, complete failure of exocrine pancreatic function may coexist with normal endocrine function. Animal studies have shown similar disturbances of exocrine pancreatic function and regeneration of the acinar epithelium following induction of acute pancreatitis[31,32].

The aetiology of graft pancreatitis is different from that of 'ordinary' acute pancreatitis in humans. The deleterious effect of ischaemia and reperfusion might be of particular importance. In the very early postoperative phase studied here, immunological reactions are not involved. Known consequences of ischaemia include exhaustion of energy metabolism, tissue acidosis and the development of oxygen free radicals[33,34]. Changes in membrane structures such as the endoplasmic reticulum, demonstrated at the end of the period of cold ischaemia, may reflect exhaustion of energy metabolism. Similar changes have been described in the human pancreas following a severe reduction in blood flow, for example due to shock or local vasospasm[35–38]. The fact that pancreatitis can be induced by ischaemia and/or hypoxia, and that oedematous inflammation can proceed to the necrotizing form, has previously been shown only in animal models[39–42]. The present results demonstrate a possible role for hypoxia in the induction of ordinary acute pancreatitis in humans[43].

Irrespective of the different aetiological factors, there is still no conclusive knowledge about the initial morphological and biochemical processes that occur in acute pancreatitis[1,2,6,28]. Whether the same sequence of morphological events occurs in all forms of acute pancreatitis in humans remains uncertain. Further morphological and biochemical studies of pancreatic graft biopsies might allow identification of the initial reactions that develop in this disease.

Acknowledgements

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Temporal relationship of acinar and microvascular changes in caerulein-induced pancreatitis

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A study in rats investigated the temporal relationship between acinar cell changes and alterations in the local microvasculature in oedematous pancreatitis produced by administration of caerulein 5 µg kg^{-1} h^{-1}. Samples were taken from experimental and control animals after 15 min, 30 min, 1 h and 2 h of caerulein infusion. Transmission electron microscopy showed ultrastructural acinar cell changes after 15 min whereas the earliest microvascular changes were seen after 30 min. Ultrastructural alterations in the acinar cells thus preceded local microvascular changes. Microvascular distortion appears to be a consequence and not a cause of pancreatitis in the caerulein model.

Caerulein-induced pancreatitis is associated with early changes in the acinar cell[1,2] and recent work has demonstrated marked distortion of the local microvasculature[3]. Studies using established models suggest that microvascular changes are critical in the pathogenesis of acute pancreatitis[3,4]. This study was undertaken to investigate the temporal relationship between acinar cell changes and alterations in the local microvasculature.

Materials and methods

Twelve male Sprague–Dawley rats weighing 350–450 g were anaesthetized with intraperitoneal chloral hydrate 36 mg per 100 g body-weight. Eight animals received an intravenous infusion of caerulein 5 µg kg^{-1} h^{-1} into the jugular vein, and four control rats received a similar volume of saline. Two experimental animals and one control rat were killed after 15 min, 30 min, 1 h and 2 h. Pancreatic samples were taken immediately after death, fixed in 2·5 per cent buffered glutaraldehyde solution, dehydrated in a graded alcohol series and embedded in Epon 812 (Agar Scientific, Stansted, UK). Ultrathin sections were cut with an LKB ultramicrotome (Leica, Cambridge, UK), stained with 2 per cent uranyl acetate followed by 1·3 per cent lead citrate, and viewed with a JEOL 200 EX electron microscope (Japanese Electron Optics Ltd, Tokyo, Japan). Multiple samples were taken from each pancreas and several sections processed from each sample.

Results

The ultrastructure of the pancreatic acini in the control rats was normal (*Figure 1*). In the experimental animals the first changes were seen after 15 min; these included vesiculation of the endoplasmic reticulum and the appearance of small cytoplasmic vacuoles (*Figure 2*). After 30 min vacuoles had increased in number. Zymogen granules of varying size and shape aggregated around the vacuoles (*Figure 3*). After 1 h of caerulein infusion the number of zymogen granules had decreased. After 2 h zymogen granules were sparse and large cytoplasmic vacuoles had developed that contained fragments of sequestered cytoplasm including zymogen granules, myelin-like figures and debris; the vacuoles in some instances were so large that they indented the cellular nuclei (*Figure 3*). Mitochondria appeared normal throughout the study period.

No abnormalities were seen in the microcirculation until 30 min after the start of caerulein infusion. The only change noted in the capillaries at this time was an increase in the number of fenestrae (*Figures 4* and *5*). After 1 h the number of micropinocytotic vesicles in the vessel walls had increased (*Figure 6*) and after 2 h there was gross irregularity of the endothelial lining of the vessel lumen (*Figure 7*). The basement membrane remained intact throughout the study. These vessels

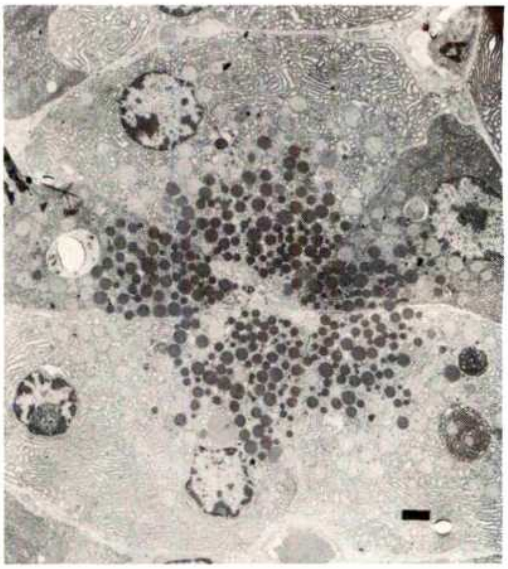

Figure 1 *Transmission electron micrograph of a normal pancreatic acinus in a control animal. (Bar 2 µm)*

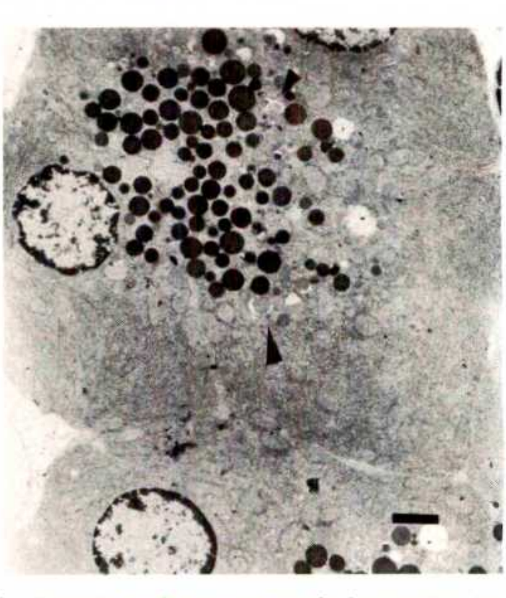

Figure 2 *Transmission electron micrograph of pancreatic acinus 15 min after the start of caerulein infusion. Several autophagic vacuoles containing cellular debris are present (arrows) in association with zymogen granules of different sizes. (Bar 2 µm)*

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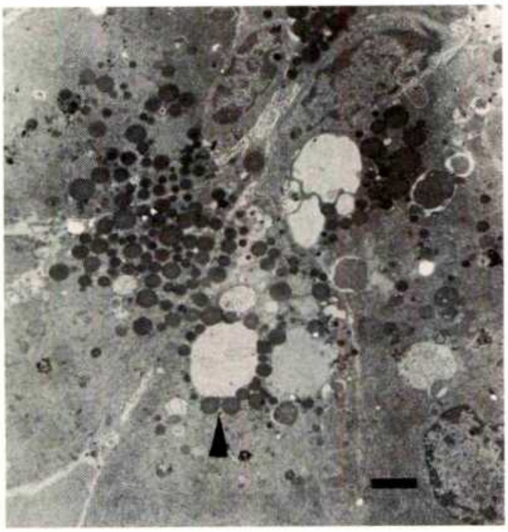

Figure 3 *After 2 h of caerulein infusion, cytoplasmic vacuoles are very large. Zymogen granules vary greatly in size and are seen aggregating around the vacuoles (arrow). (Transmission electron micrograph, bar 2 μm)*

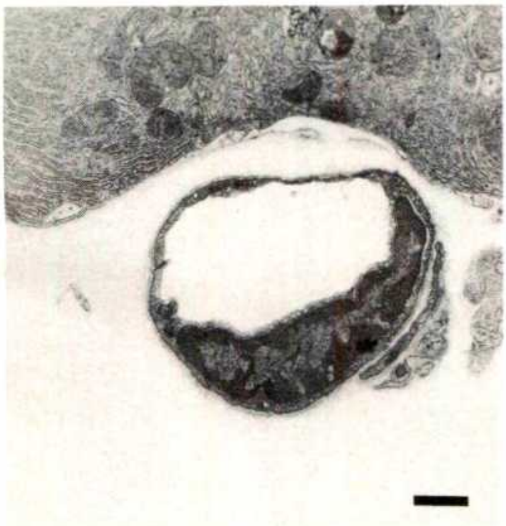

Figure 4 *Transmission electron micrograph showing a cross-section through a pancreatic capillary in a control animal. Note the flat regular endothelium with scattered micropinocytotic vesicles, which was characteristic of the vessels in these animals. (Bar 1·5 μm)*

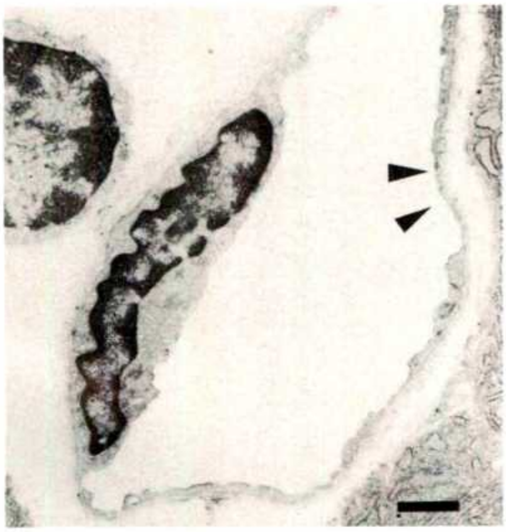

Figure 5 *Transmission electron micrograph showing a cross-section through a pancreatic capillary after 30 min of caerulein infusion. Note the increased number of fenestrae present (arrows) in comparison with the control vessel. (Bar 1·5 μm)*

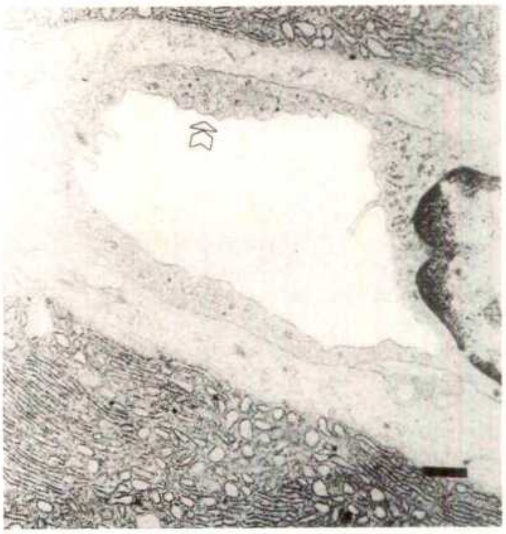

Figure 6 *After 1 h of caerulein infusion there was a marked increase in the number of micropinocytotic vesicles (arrow). (Transmission electron micrograph, bar 0·5 μm)*

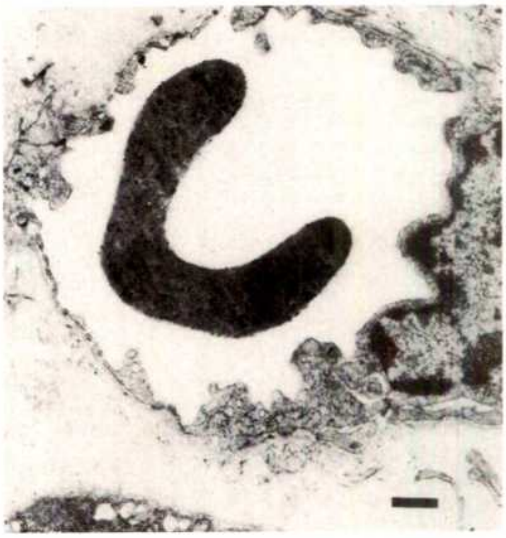

Figure 7 *Transmission electron micrograph of a pancreatic capillary after 2 h of caerulein infusion. The endothelial lining is grossly irregular and a large number of fenestrae are present. (Bar 1·5 μm)*

also contained numerous red blood cells but showed no evidence of intravascular thrombosis. These findings were consistent in all sections studied and in all of the experimental animals.

Discussion

The pathogenesis of acute pancreatitis remains unclear. There is universal agreement on many of the major ultrastructural acinar cell changes that accompany acute pancreatitis, and the alterations described in the present study are characteristic of the model[4,5]. As pointed out by Adler and colleagues[5], no clear distinction has been made between factors that initiate acute pancreatitis and those that occur as a result of injury and subsequently play a role in further progression of the disease.

Possible involvement of the local microvasculature in the pathogenesis of acute pancreatitis was first recognized by Panum in 1862. Since then, numerous authors have confirmed the importance of vascular factors in pancreatitis[6,7] and in extrapancreatic organ impairment[8,9]. Workers using the *ex vivo* pancreatitis model[10] have demonstrated an early increase in capillary permeability. Recent experimental work using microvascular casting has confirmed that significant distortion of the local microvasculature occurs early in caerulein-induced pancreatitis[3], but the role of these changes in the pathogenesis of the disease remains unclear.

The vascular endothelium of visceral capillaries transports molecules by transcytosis. This occurs through vesicles, vacuoles and fenestrae[11]. The vascular features of an increased number of fenestrae, micropinocytotic vesicles and irregularity of the endothelial lining as seen in the present study are consistent with increased transport across the cell membrane[11]. This type of transport is specialized for water and solutes but whether the increased activity represents increased transport of fluid and other constituents from the periacinar spaces to the circulation is unclear.

Although the number of rats studied at each time interval is small (two experimental, one control), the present findings correspond closely with previous experimental work, which evaluated intra-acinar and microvascular changes in the same model separately[4,5]. The present observations demonstrate that acinar cell changes precede vascular changes. This is in contrast to previous work[10] and suggests that, in the caerulein model, vascular changes are not the critical initiating factor in the pathogenesis of disease.

Acknowledgements

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Resection for adenocarcinoma of the body and tail of the pancreas

Adenocarcinoma of the pancreatic body and tail often presents late and is widely regarded as incurable by surgical resection; long-term survivors are rare. Thirteen patients underwent left resection (n = *7) or total pancreatectomy* (n = *6) in a consecutive series of 105 patients with carcinoma of the body or tail of the pancreas. Comparison was made with 17 patients with locally advanced or metastatic disease. Preoperative computed tomography predicted irresectable disease when a large perivascular lymph node mass was demonstrated. Preoperative angiography predicted irresectable disease when there was encasement or obliteration of the coeliac axis or its major branches, or of the superior mesenteric artery or vein. Splenic vessel involvement was sometimes compatible with resection. After resection, median survival was 13 (range 3–50) months, with a minimum follow-up of 2 years. Five patients survived more than 2 years, and three are still alive 30, 43 and 50 months after resection. Resection of carcinoma of the body or tail of the pancreas was possible in 12 per cent of patients and long-term survival was observed in some of these.*

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Pancreatic adenocarcinoma has a poor prognosis. Most tumours arise in the head of the gland and patients present with obstructive jaundice. Patients with tumours of the body and tail often present late because of the vague non-specific symptoms and the absence of localizing features such as jaundice[1].

The purpose of this study was to review experience of adenocarcinoma of the body and tail of the pancreas. In recent years a more aggressive policy toward resection of these tumours has been pursued, with some encouraging results.

Patients and methods

A prospective record of all pancreatectomies for adenocarcinoma of the pancreas has been kept in the University Surgical Unit, Mannheim, since October 1972. In January 1992, all patients operated on before 1 January 1990 were reviewed. All those who underwent resection of adenocarcinoma of the pancreas arising to the left of the superior mesenteric vein were included. Patients with adenocarcinoma of the head of the pancreas who underwent Whipple's resection or total pancreatectomy were excluded. The operating records for 1988 and 1989 were inspected to identify patients with carcinoma of the body and tail of the pancreas who did not undergo resection. These years were chosen as they provided a sufficient number of adequately assessed patients for comparison with those undergoing resection.

Records of patients who underwent resection and those without liver metastases who did not were compared to try to identify features that might predict irresectability. Preoperative computed tomography (CT) and angiography were performed according to clinical indications and availability of the techniques. Radiologists' reports were scrutinized, with particular attention to features that might indicate resectability or irresectability. These features were compared with the surgeon's record of the operative findings.

All patients who underwent resection were followed prospectively. No patient was given adjuvant therapy after resection. Dates of recurrence of tumour and survival times were recorded. Patients who did not undergo resection were generally discharged from follow-up; information was sought from their family doctor about recurrence, further symptoms and length of survival.

Because of the small number of patients with resectable adenocarcinoma of the body and tail of the pancreas, life-table analysis was not used. The results are presented as brief clinical details, giving survival times for each patient.

Results

From 1 October 1972 to 31 January 1989, 709 patients with histologically verified adenocarcinoma of the pancreas were treated. In 604, the tumour was in the head of the gland. Of these, 142 patients (24 per cent) underwent pancreatoduodenectomy.

There were 105 patients with adenocarcinoma of the pancreatic body (63 patients) or tail (42); of these, 13 (12 per cent) underwent resection. In six cases this required total pancreatectomy, with resection of the portal vein in three. Seven patients underwent left-sided pancreatectomy (left hemipancreatectomy in six, subtotal resection in one). One of these patients required total gastrectomy for tumour invasion, one left nephrectomy for invasion of perinephric fat and two resection of tumour invading directly into the transverse mesocolon or by metastasis into the greater omentum.

For comparison, 17 patients were identified who were found at laparotomy to have irresectable adenocarcinoma of the body or tail of the pancreas. There were ten patients with locally advanced and histologically confirmed adenocarcinoma. Eight of these tumours definitely arose in the pancreas. In two cases the clinical impression was of a pancreatic tumour, but the histology was not diagnostic of the organ of origin. Seven further patients were found to have pancreatic adenocarcinoma of the body and tail with liver metastases.

The age and sex ratio of the different groups were similar (*Table 1*). In this retrospective survey it was not possible to determine any difference in the clinical features between patients suitable for resection and those with locally advanced disease. Pain in the upper abdomen and left upper quadrant was a common feature and weight loss was frequently seen. In

Table 1 *Age and sex distribution of patient groups*

	Median (range) age (years)	Sex ratio (M:F)
Total pancreatectomy (*n* = 6)	58 (43–65)	5:1
Left-sided pancreatectomy (*n* = 7)	68 (49–77)	4:3
Tumour irresectable because of local invasion (*n* = 10)	61 (55–78)	5:5
Liver metastases (*n* = 7)	64 (33–74)	2:5

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Table 2 *Pathological diagnosis, tumour stage and survival in 13 patients who underwent resection of ductal adenocarcinoma of the body or tail of the pancreas*

Patient no.	Histological diagnosis	Stage*	Survival (months)
Distal resection			
1	Adenocarcinoma	$T_2 N_1$	>30†
2‡	Papillary ductal adenocarcinoma	$T_3 N_0$	8
3§	Schirrhous papillary ductal carcinoma	$T_3 N_1$	6
4	Ductal adenocarcinoma	$T_2 N_1$	26
5	Ductal adenocarcinoma	$T_2 N_1$	18
6	Ductal adenocarcinoma	$T_2 N_1$	7
7	Ductal adenocarcinoma	$T_2 N_0$	25
Total pancreatectomy			
8	Ductal adenocarcinoma	$T_3 N_1$	3
9	Ductal adenocarcinoma	$T_2 N_0$	>50†
10	Ductal adenocarcinoma	$T_2 N_0$	>43†
11	Ductal adenocarcinoma	$T_2 N_1$	13
12	Ductal adenocarcinoma	$T_3 N_1$	8
13	Ductal adenocarcinoma	$T_3 N_1$	11

*T_2, primary tumour 2–5 cm; T_3, tumour >5 cm; N_0, no involved lymph nodes; N_1, local peripancreatic nodes involved. †Patient still alive. ‡Patient underwent total gastrectomy and omentectomy; §patient underwent left nephrectomy and adrenalectomy in addition to left pancreatectomy

particular, there was no apparent difference in the duration of symptoms before diagnosis.

Four patients did not undergo endoscopic retrograde cholangiopancreatography. In the remainder, all but one showed abrupt occlusion of the pancreatic duct in the body or tail. Both CT and angiography were useful predictors of inoperability. On CT, the finding of a large mass extending beyond the pancreas with involvement of other organs usually, but not always, predicted irresectability. The presence of enlarged lymph nodes in the para-aortic, coeliac trunk and superior mesenteric areas also helped to predict irresectability. Angiography correctly predicted irresectability whenever there was occlusion or encasement of the superior mesenteric artery, common hepatic artery or coeliac trunk. Occlusion of the superior mesenteric vein on angiography was also a sign of irresectability. Encasement of the splenic artery and occlusion of the splenic vein were not absolute indicators of inability to perform resection. On two occasions, occlusion of the splenic vein was demonstrated in resectable tumours, although both of these lesions were large (>5 cm) with invasion into peripancreatic connective tissue. Resection of these tumours required subtotal pancreatectomy, with total gastrectomy in one case and left pancreatectomy plus excision of mesocolon in the other.

All patients who underwent resection had histologically confirmed pancreatic adenocarcinoma. Tumour type and stage are shown in *Table 2*.

Outcome

There were no postoperative deaths following resection. Two postoperative fistulas developed after left-sided pancreatic resection; one required multiple drainage procedures and the other closed but required a single drainage of a pancreatic fluid collection 3 months after operation. One patient is still alive with recurrence after left pancreatic resection. One patient required gastroenterostomy and another insertion of an endoprosthesis for obstructive jaundice. Patients with advanced (T_3) tumours generally had a poor prognosis, despite extensive resection of adjacent organs (*Table 2*).

After total pancreatectomy, two patients remain well with no evidence of tumour recurrence 43 and 50 months after surgery. Four patients have died from recurrence, 3–13 months after resection. Thus, in this highly selected group of six patients, two have survived more than 3 years.

Overall, the numbers surviving following resection of tumours of the body and tail were seven of 13 at 1 year, five at 2 years and two at 3 years.

Survival after laparotomy only

As expected, survival was uniformly short in patients with liver metastases: median 4 (range 2–9) months. All patients with irresectable locally invasive tumours died, at a median of 8 (range 2–15) months after operation. Only one patient survived more than 12 months.

Discussion

This study shows that, in a small selected group of patients with localized tumours of the body and tail of the pancreas, resection appears to be worthwhile, with relatively prolonged survival.

Two large series[2,3] of carcinoma of the body and tail of the pancreas reported resection rates below 8 per cent. The higher resection rate in the present series may represent improvement in diagnostic imaging with ultrasonography and CT, or perhaps may reflect a changing referral pattern. Nevertheless, the resection rate is still only half that for cancer of the pancreatic head in this unit[4], suggesting that there may be room for further improvement.

The low resection rate generally reported reflects the considerable pessimism felt about tumours of the body and tail of the pancreas. Very few survivors beyond 1 year have been recorded: Moossa[5] found only one in a 45-year literature review, and one of seven patients who underwent resection in a Japanese series[3] lived for 18 months. A recent review[1] concluded: 'the message is clear: ductal cancers distal to the head of the pancreas are virtually incurable'. Nevertheless, it seems reasonable to suppose that, if a patient presents with a resectable tumour, survival may be prolonged by a resection, even if ultimate cure cannot be achieved. This has been the authors' experience, with over half of patients who underwent resection surviving more than 1 year and 38 per cent surviving more than 2 years, despite the absence of very early (T_1) tumours. A recent report from the Mayo Clinic[6] supports the view that resection may be valuable, particularly in patients with tumours confined to the pancreas. Median survival in 26 patients who underwent resection of carcinoma of the body or tail of the pancreas was only 10 months, but two patients survived 5 years. A further case report[7] recorded a patient with poorly differentiated ductal adenocarcinoma who was alive and well 6 years after distal pancreatectomy.

A further argument in favour of resection is that it provides good palliation. Excision of a localized tumour will generally avoid the need for subsequent gastroenterostomy, as obstruction at the duodenojejunal flexure is uncommon after resection. In the present series, one of 13 patients has required subsequent gastroenterostomy. Three of ten patients with inoperable tumours required gastroenterostomy at the time of presentation.

A final decision about resectability in doubtful cases can be made only at operation. The value of preoperative investigation is in the identification of patients whose tumour will definitely be irresectable. A combination of CT and angiography can identify such patients. A large tumour mass extending outside the pancreas may be resectable if it does not involve major vascular structures outside the planned field of resection. Particular signs of irresectability are demonstration on CT of tumour involvement or lymph node enlargement around the coeliac trunk. Similarly, angiographic evidence of encasement of the coeliac trunk, common hepatic artery or left gastric artery, and of the superior mesenteric artery, also suggests irresectability. Occlusion of the superior mesenteric vein was also associated with an irresectable tumour, but three patients with involvement of the portal vein by tumour and otherwise localized disease were treated by resection of the tumour and portal vein in continuity, and interposition of a vascular graft. None of these patients survived beyond 12 months.

Evidence of involvement of the splenic artery and vein is not an absolute contraindication to resection. These vessels will be removed along with the pancreas, so that involvement with tumour is not in itself of importance. However, these radiographic signs were associated with large and invasive tumours at the limit of resectability. Both patients with splenic vessel occlusion sustained early local recurrence, with death at 6 and 8 months.

Tumour size also predicts local recurrence. The two patients with splenic vein thrombosis and early local recurrence both had tumours in excess of 5 cm in diameter. Four patients with a T_3 tumour died within 8 months of resection and the fifth after 11 months. However, the 6-year survivor noted by Billesbolle *et al.*[7] had a tumour measuring 11 × 10 × 7 cm, so such patients should not be denied resection if it is feasible.

The choice of operation for a tumour of the body or tail of the pancreas depends on its anatomical position. Tumours in the tail or at the junction of the body and tail are likely to be resectable with a conventional left-sided pancreatectomy, dividing the gland in front of the portal vein. Those of the body are more likely to encroach on the pancreatic neck and, if the patient is in a suitable general condition, total pancreatectomy is recommended for such lesions.

Aggressive surgical management of pancreatic adenocarcinoma can be justified only if there is a reasonable prospect of survival beyond 1 year and if operative mortality is minimal. If survival is generally less than 1 year, it is arguable that the patient has achieved little benefit from operation. If the operative mortality rate is high, any potential benefit of prolonged survival is cancelled out. In this unit, the operative mortality rate for resection of the pancreatic head is less than 3 per cent[8], with no deaths in over 150 consecutive pancreatoduodenectomies[4]. There were no postoperative deaths in the present 13 patients who underwent either total or left pancreatectomy.

The present results give a faint hope that resection may offer benefit to patients with localized adenocarcinoma of the body or tail of the pancreas. No firm conclusions can be drawn from the comparison with patients who did not undergo resection because, by definition, they had a more advanced stage of disease. Nevertheless, the observation that seven of this selected group of 13 patients survived beyond 1 year is encouraging. After total pancreatectomy, two patients survived more than 3 years.

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Laparoscopic cholecystectomy in the Netherlands

Laparoscopic cholecystectomy was introduced into the Netherlands in the Spring of 1990. The aim of this study was to evaluate the results of the procedure in Dutch hospitals over the first 2 years to obtain some insight into its safety and efficacy in general surgical practice. A written questionnaire was sent to all 138 Dutch surgical institutions enquiring about conversion rate, complications (with emphasis on mortality rate and common bile duct injuries), operating time and hospital stay. The surgeons' opinions were also sought on possible contraindications such as previous operation, bile duct stones and cholecystitis, as were their estimations of the percentage of patients in their practice eligible for laparoscopic cholecystectomy. Data were obtained for 6076 laparoscopic cholecystectomies; the response rate was 100 per cent. Conversion to open cholecystectomy was necessary in 413 patients (6·8 per cent), mostly because of adhesions, cholecystitis, haemorrhage and unclear anatomy. Postoperative complications were reported in 260 patients (4·3 per cent). There were seven deaths (0·12 per cent) and 52 (0·86 per cent) bile duct injuries, of which 20 were recognized during laparoscopy. The mean operating time for the ten most recent patients in each institute was 70 (range 30–180) min and the mean hospital stay 4·5 (range 2–8) days. Previous lower abdominal operations were not considered to be a contraindication by 96 per cent of surgeons, whereas previous upper abdominal procedures were regarded as a contraindication by 66 per cent. After successful clearance of the bile duct at endoscopic retrograde cholangiopancreatography, only 12 per cent would perform an open procedure. Moderate cholecystitis was not considered a contraindication to laparoscopic cholecystectomy by 71 per cent of surgeons, but severe cholecystitis was a reason for open cholecystectomy for 83 per cent. In most surgical practices 70–80 per cent of patients were considered to be eligible for the laparoscopic procedure. In conclusion, laparoscopic cholecystectomy has gained rapid acceptance in the Netherlands. Although the number of bile duct injuries is high, the findings of this general survey are similar to those from highly specialized centres and match the overall results of conventional cholecystectomy.

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In the Spring of 1990, laparoscopic cholecystectomy was introduced into the Netherlands, a country with 15 million inhabitants and an annual mean of 14 000 cholecystectomies[1]. The technique was adopted from Belgian, French and American colleagues. In the Autumn of 1990 several practical courses using an animal model were started, which accelerated the diffusion of the technique throughout the country. In addition to these courses, surgeons learned from colleagues or visited facilities with expertise in laparoscopic cholecystectomy. Certification was not issued, nor was it officially required.

Initial reports of a reduction in operative morbidity in laparoscopic compared with conventional cholecystectomy and patient demand provoked by the media stimulated rapid diffusion of the technique among Dutch surgeons. Most of the results reported in the literature are selected series from centres with extensive experience[2–4]. Limited data are available on the results of laparoscopic cholecystectomy in general surgical practice[5,6]. Results for the non-selected general patient population, previously treated by conventional cholecystectomy, should be collected to demonstrate the safety and efficacy of laparoscopic cholecystectomy for the general population. This study is a review of the results of laparoscopic cholecystectomy throughout the Netherlands over the 2-year period since its introduction.

Patients and methods

A written questionnaire requesting surgical data on laparoscopic cholecystectomy was sent to all 138 surgical institutions in the Netherlands. These institutions include eight university centres, 28 teaching hospitals and 102 community hospitals. The period covered by the survey extended from the first laparoscopic cholecystectomy performed in the Netherlands, in February 1990, to the start of the survey, in April 1992. Questions included the total number of laparoscopic cholecystectomies performed during that period, the number of conversions to the open procedure and the indications for this policy. Other questions related to postoperative complications, with the emphasis on common bile duct (CBD) injuries and deaths, as well as the mean operating time for the most recent ten procedures (or fewer if experience was limited) and the mean hospital stay including the day of admission and day of discharge.

The surgeons' opinions were sought on possible contraindications for laparoscopic cholecystectomy, particularly previous operations, CBD stones and cholecystitis. Finally, surgeons were asked to estimate the percentage of patients in their practice eligible for the laparoscopic procedure.

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Results

A questionnaire compliance rate of 100 per cent was achieved. Completed forms were received from 103 institutions and data from the other 35 were collected by means of personal telephone calls to the surgeons.

In 134 of the 138 institutions 6076 laparoscopic cholecystectomies were performed during the period covered. A mean of 45 (range 1–230) procedures had been performed in each institution. Laparoscopic cholecystectomy was performed by one or two surgeons from the practising group in each hospital.

Conversion to an open procedure was necessary in 413 patients (6·8 per cent) (*Table 1*). The indications were mainly adhesions and cholecystitis. Haemorrhage, unclear anatomy, bile leakage from the gallbladder and certain technical problems were initially major reasons for laparotomy, but this changed as experience grew.

Postoperative complications were reported in 260 patients (4·3 per cent) (*Table 2*). Bile leakage was observed as leakage from the wound drain or as a fluid collection at postoperative ultrasonography, but this rarely resulted in laparotomy. The majority of haemorrhagic complications consisted of a fall in postoperative haemoglobin level that did not necessitate surgical intervention. CBD injuries were reported in 52 patients (0·86 per cent). Twenty of these were detected during the procedure and were corrected immediately; 32 lesions were found after surgery.

There were seven deaths (0·12 per cent). After repair of a laparoscopic CBD injury, three patients died from septicaemia, massive gastrointestinal haemorrhage and pulmonary embolus. Two patients died from myocardial infarction, one from incorrectly assessed bleeding from the cystic artery and one from rapidly spreading *Clostridium perfringens* septicaemia following a cystic duct leakage.

Table 1 *Indications for conversion to an open procedure during laparoscopic cholecystectomy*

	No. of patients
Adhesions	115
Haemorrhage	80
Cholecystitis	72
Unclear anatomy	66
Common bile duct injury	20
Bile leakage	22
Technical problem	15
Problems with instruments	12
Carcinoma	5
Iliac artery injury	2
Vena cava injury	2
Bowel perforation	1
Pneumothorax	1

Table 2 *Surgical complications after laparoscopic cholecystectomy*

	No.
Bile leakage	49
Common bile duct injury	32
Retained stones	6
Pancreatitis	1
Incomplete gallbladder removal	1
Wound infection	79
Intra-abdominal abscess	21
Haemorrhage	46
Pneumonia or atelectasis	8
Pneumothorax	1
Incisional hernia at umbilicus	5
Incisional hernia in epigastrium	2
Colonic perforation	2
Transient ischaemic attack	1
Congestive heart failure	2
Cardiac ischaemia	1
Pulmonary emboli	2
Deep vein thrombosis	1

Table 3 *Surgeons' opinions on contraindications to laparoscopic cholecystectomy*

	Contraindication	
	Yes (%)	No (%)
Previous lower abdominal procedure	4	96
Previous upper abdominal procedure	66	34
CBD stones *in situ*	89	11
CBD stones cleared after successful ERCP	12	88
Moderate cholecystitis	29	71
Severe cholecystitis	83	17

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography

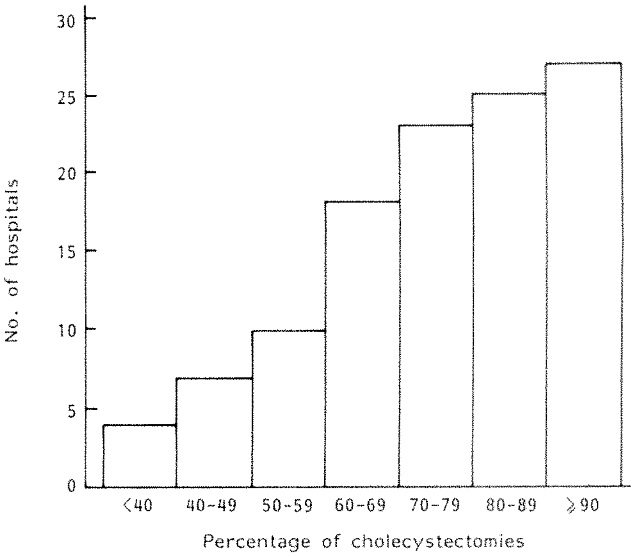

Figure 1 *Response of surgeons representing each group to the question: 'What percentage of cholecystectomies can be performed laparoscopically in your surgical practice?' About 15 per cent of surgeons had no opinion, mostly because of limited experience with the laparoscopic procedure*

The mean operating time was 70 (range 30–180) min. In centres with experience of fewer than 15 procedures, the mean operating time was 100 (range 55–200) min. This decreased to 66 (40–90) min after more than 15 procedures. The mean hospital stay was 4·5 (range 2–8) days.

Surgeons' opinions on contraindications for laparoscopic cholecystectomy are presented in *Table 3*, showing a range from absolute to relative contraindications. *Figure 1* shows the surgeons' rather divergent estimates of the percentage of patients who would be eligible for laparoscopic cholecystectomy.

Discussion

In this survey, 100 per cent compliance could be obtained because the Netherlands is a relatively small country with a coherent surgical group. After the introduction of laparoscopic cholecystectomy, surgeons from more than half of the hospitals were taught at the authors' centre, which obviously facilitates communication. Laparoscopic surgery is still in its early stages, with a mean experience of 45 cholecystectomies per hospital. The great interest in these procedures has contributed to accurate data registration. Limitations on the ability to request detailed information which is difficult to retrieve over a broad area were accepted to achieve high compliance and reliable data in this national survey.

Over 2 years after its introduction, almost all Dutch institutions now perform laparoscopic cholecystectomy; the exceptions are one cancer centre and three community hospitals. Most of the surgical teams started laparoscopic surgery during 1991. The experience of each hospital varies widely and is affected by the availability of laparoscopic equipment. More than one-third of hospitals performed procedures with instruments on loan from companies.

In view of the relatively limited experience, a conversion rate of 6·8 per cent is acceptable. In the early stages, surgeons show a low threshold for conversion to the open procedure. As experience grows, adhesions, cholecystitis, minor haemorrhage, technical problems and gallbladder perforations are less likely to lead to conversion.

The mortality rate was 0·12 per cent. In five of the seven patients, death was related to complications of laparoscopic cholecystectomy: in three to CBD injury, in one to cystic artery haemorrhage and in one to septicaemia following bile leakage. McSherry and Glenn[7] reported a 0·5 per cent mortality rate in non-complicated cholecystectomy caused mainly by cardiovascular disease. If laparoscopic cholecystectomy becomes routine, even lower surgical mortality rates can be expected than those reported in the present survey.

Complications of laparoscopic cholecystectomy can be related to laparoscopy, cholecystectomy or surgical procedures in general. Morbidity related to laparoscopy consists mainly of vascular or bowel injury due to insertion of the trocar and cannula and of pneumothorax as a result of the pneumoperitoneum, which occurred in nine (0·15 per cent) of 6076 patients. Despite the general use of cannulas with a safety shield for the first insertion, injuries do still occur. Insufficient pneumoperitoneum, usually during reinsertion of the trocar and cannula, reduces the distance between the abdominal wall and intra-abdominal structures, leading to injury. In cases of pneumothorax a relatively high intra-abdominal pressure (15 mmHg or higher) was used; this should be avoided.

Complications related to cholecystectomy consist of haemorrhage, CBD injury, bile leakage and retained stones. Severe haemorrhage during operation can be salvaged by conversion to laparotomy. One patient died because of an incorrectly evaluated cystic artery haemorrhage immediately after operation. This argues for overnight monitoring of the patient after laparoscopic cholecystectomy. Bile duct injuries are a major complication, detected in 20 patients during laparoscopy and 32 after surgery. The figure of 0·86 per cent CBD injuries found in the present study is higher than the 0·2–0·3 per cent reported for conventional cholecystectomy[8]. In the early stages, rates of approximately 1 per cent for CBD injury were reported by several authors[3,9,10]. The fact that the present study includes the early experience of all centres in one country might explain the relatively high incidence of bile duct injury. A decrease with time may be expected. Three patients died from complications of the CBD injury; these injuries were all detected after operation. If an injury is suspected during laparoscopy, operative cholangiography can demonstrate it and immediate treatment is then mandatory. Bile leakage was usually managed without a second procedure and can be detected after operation by the combination of abdominal pain in the right upper quadrant and a subhepatic fluid collection shown by ultrasonography or leakage demonstrated by cholescintigraphy.

The low number of retained stones reported in the survey may reflect the preoperative selection criteria, which included the absence of signs of CBD stones. Furthermore, the follow-up has been short and the incidence might be underestimated. Operative cholangiography is not routine during laparoscopic cholecystectomy in the Netherlands.

Morbidity related to surgical procedures in general consisted of wound infection, and pulmonary, cardiac and thromboembolic complications. The infection rate of 1·65 per cent is lower than that in conventional cholecystectomy. Although two patients died from myocardial infarction, the number of general complications was low. Incisional hernia occurred in five patients at the umbilical site and in two at the epigastric cannula insertion site. Since the gallbladder is usually extracted through the umbilical incision, which is sometimes enlarged, separate fascial closure is recommended.

The mean operating time decreased from 100 min for the first 15 procedures to approximately 1 h, which indicates a 'learning curve'. The mean hospital stay, including the day of admission and that of discharge, was 4·5 days, which implies that there has been a reduction in the hospital stay for complicated and uncomplicated cholecystectomy in the Netherlands: the mean stay was 13·5 days before the introduction of laparoscopic cholecystectomy.

At the introduction of laparoscopic cholecystectomy, a previous laparotomy, CBD stones and cholecystitis were assumed to constitute relative contraindications. The present Dutch surgeon's opinion is more liberal. Previous lower abdominal incision is hardly felt to be a contraindication, but there is some reserve with regard to upper abdominal operations. With the back-up of an experienced gastroenterologist to perform endoscopic retrograde cholangiopancreatography, CBD stones are generally not felt to be a major contraindication for laparoscopic cholecystectomy. Still, most surgeons prefer prior clearance of the bile duct before attempting the operation. The eligibility of patients for a laparoscopic approach to cholecystitis depended on the surgeon's experience. Surgeons estimated that 70–90 per cent of patients with gallstone disease would benefit from laparoscopic cholecystectomy.

In conclusion, laparoscopic cholecystectomy is rapidly being implemented in the Netherlands. Although no accreditation system exists, the procedure is relatively safe in general surgical practice. The number of conversions and serious complications such as bowel injury by the trocar and cannula and CBD injury are expected to decrease as most of the surgical institutions have passed the lag phase of the 'learning curve'. The anticipated reductions in surgical morbidity rate and hospital stay will benefit 70–90 per cent of patients with gallstone disease in the Netherlands over the next few years.

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Surgical workshop

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Pancreatoduodenectomy with stapling devices

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Surgical stapling instruments have found wide application, particularly in gastrointestinal procedures[1,2]. Their use in pancreatic surgery has not been great, although encouraging clinical results[3,4] in distal pancreatectomy were published more than 10 years ago. In a consecutive series of 26 Whipple procedures, the usefulness of TA55 and GIA50 staplers (US Surgical, Norwalk, Connecticut, USA) for transection and anastomosis of the pancreas has been evaluated. The indications for surgery were pancreatic cancer (13 patients), ampullary carcinoma (six), cancer of the common bile duct (one) and chronic pancreatitis (six).

Surgical technique

The pancreas was prepared by blunt dissection between the gland and portal vein so that the surgeon's finger could pass easily between them. The TA55 stapler was loaded with a 3·5- or 4·8-mm cartridge, depending on the thickness of the pancreas. The opened jaws were passed around the pancreas and a double line of stainless steel staples placed across the gland. The pancreas was then divided with a knife, using the cartridge as a cutting guide.

The jejunum was divided 5 cm distal to the duodenal flexure with the GIA50 stapler. Pancreatojejunostomy was performed by approximating the stapled jejunum to the stapled pancreas. A single layer of interrupted atraumatic sutures was placed between the pancreatic capsule and the jejunum, 5 mm posterior to the staple line. By knotting the stitches, the pancreas was attached to the jejunum to complete the posterior aspect of the anastomosis. Next, two staples at the site of the pancreatic duct and the corresponding site of the jejunum were removed to provide drainage of pancreatic juice into the jejunum. The anastomosis was completed by an anterior layer of sutures, as described for the posterior layer.

Results

The technique was applicable in 24 of the 26 patients. In one patient with chronic pancreatitis and another with locally advanced pancreatic cancer it was not possible to encompass the pancreas with the TA55 stapler.

In no instance did stapling the pancreas damage the parenchyma. Minor bleeding from the staple line was observed in 13 patients but stopped spontaneously in the majority of cases. One 72-year-old patient died from cardiac failure on day 4 after operation; the pancreatic bed was unremarkable at autopsy. There were five complications: re-exploration for haemorrhage (one) and wound infection (four). No pancreatic fistula arose and no patient developed exocrine or endocrine pancreatic insufficiency within a follow-up of 20 months.

This technique provides a simple, safe and quick way of transecting the pancreatic parenchyma. The uniform closure of the pancreas and jejunum provides excellent preparation for the pancreatojejunostomy, and may contribute to a reduced morbidity rate.

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New technique of open laparoscopy

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Laparoscopic cholecystectomy has become a routine procedure. Introduction of a Veress needle to establish pneumoperitoneum and subsequent blind insertion of the subumbilical trocar with cannula carry a definite risk that is clearly higher in patients who have undergone previous surgical operations. Safety guards incorporated into trocars reduce the risk but, as will be appreciated during laparoscopic visualization of trocar insertion, the protective sleeve may be held back by the peritoneum until the trocar has advanced well into the abdominal cavity. Gut and vascular injury are not uncommon[1].

Open laparoscopy using a Hasson cannula was developed to obviate the need for blind puncture with a Veress needle and subsequent blind insertion of the subumbilical trocar. A technique of open laparoscopy well suited to laparoscopic surgery is described.

Surgical technique

A Veress needle is not used. A 2-cm skin incision is made as usual in the subumbilical position. The linea alba, which is picked up using a pair of tissue-holding forceps, is divided with scissors. The peritoneum is held with a pair of haemostats, and a 1-cm opening is made with scissors. A finger is pushed through the opening and swept around the posterior aspect of the anterior abdominal wall to confirm that it is free of adherent intra-abdominal contents. A purse-string suture is placed around the opening using Ethibond (Ethicon, Edinburgh, UK) on a J shaped needle. A 10-mm cannula is inserted into the opening without a trocar. A single knot is tied on the purse-string suture so that it holds the cannula tightly (*Figure 1*). A rubber tube of about 5 cm length is created by division of the middle portion of a simple red-rubber Jaques' catheter. The ends of the purse-string suture are passed through it and the rubber tube is 'snugged down' with a haemostat on to the cannula, holding it tightly (*Figure 2*). This manoeuvre forms an adequate seal to withstand pneumoperitoneum of 12 mmHg pressure. During extraction of the gallbladder the rubber tube is removed and the purse-string suture loosens. It is then a simple matter to tighten the purse string and obtain an adequate closure of the opening in the linea alba.

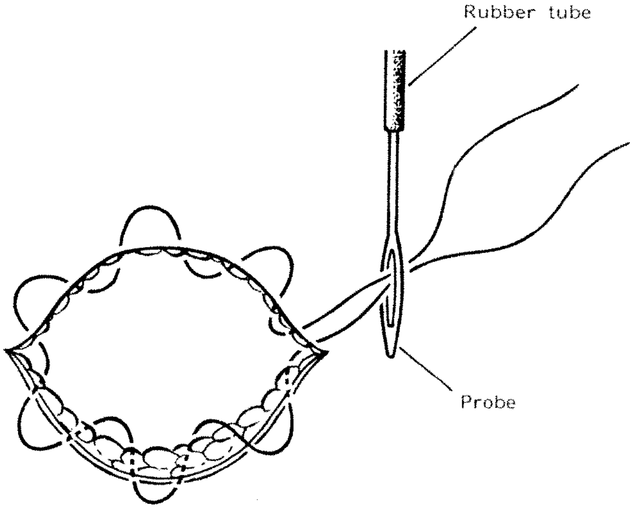

Figure 1 *The carefully placed purse-string suture*

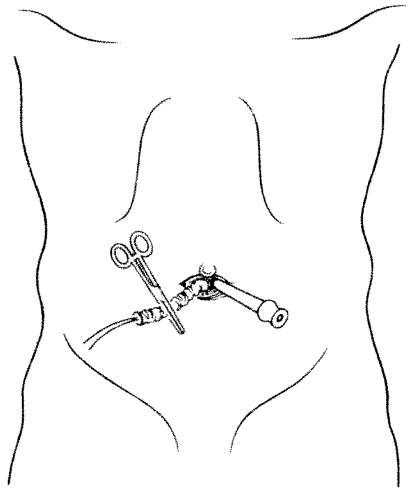

Figure 2 *The rubber tube snugged down on the 10-mm port (size of subumbilical wound enlarged for clarity)*

Discussion

Use of an endotracheal tube with insufflation of its balloon for prevention of gas leak[2] and of a grooved director for easy extraction of the gallbladder[3] have recently been reported. The method described obviates the need for the use of these methods. Advantages of the technique include: (1) less chance of injury to intra-abdominal structures, especially in patients with previous operations; (2) easy extraction of the gallbladder with stones by release of the purse string; and (3) easy and secure closure of the linea alba after extraction of the gallbladder.

The technique does not involve a larger skin incision, and there is no gas leak from the wound if the purse-string suture is placed accurately.

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Percutaneously placed Wallstent endoprosthesis in patients with malignant distal biliary obstruction

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Seventy-five patients with malignant distal biliary obstruction were treated by percutaneously placed self-expandable Wallstent endoprostheses for palliative drainage. The stent diameter was 1 cm and its length 3·5–10·5 cm. Early complications occurred in 16 patients (21 per cent); they were related to the endoprosthesis in five (7 per cent) and serious in six (8 per cent). The 30-day mortality rate was 15 per cent, with a 1 per cent procedure-related mortality rate. Sixty-five patients died 6–365 (median 87) days after stent insertion and four had recurrence of obstruction after 21–341 (median 152) days. Reobstruction was the result of tumour ingrowth in one patient, angling of the stent in one and an unestablished cause in two. Ten patients were alive without obstruction 31–383 (median 65) days after stent insertion. Percutaneous use of the Wallstent endoprosthesis allows easy insertion; reobstruction is rare.

Inoperable malignant non-hilar biliary obstruction may be palliated by endoscopic or percutaneous insertion of an endoprosthesis. Currently available plastic prostheses frequently block with sludge and, less commonly, migrate. Changes in stent design to reduce blockage rates have met with only limited success[1].

Self-expandable metallic endoprostheses have recently been introduced[2]. These have a large inner diameter after release; this is an important factor in prolonging stent patency[3]. The expansile force of the stent against the bile duct wall prevents migration. The Wallstent endoprosthesis (Wallstent; Schneider, Bülach, Switzerland) used in the present study is composed of a stainless steel braided self-expandable mesh and is loaded in compressed form on a small (7 Fr) delivery catheter, to be released by progressive withdrawal of the enclosing membrane. Experience with the Wallstent endoprosthesis and its role in the stenting of malignant distal biliary stricture are described.

Patients and methods

Between 1989 and 1991, 75 patients with inoperable malignant biliary obstruction distal to the liver hilum were treated by percutaneous insertion of a Wallstent endoprosthesis. There were 36 men and 39 women with a median age of 72 (range 36–91) years. Fifty-three patients had pancreatic carcinoma, four cholangiocarcinoma, 12 periportal metastasis and six obstruction due to miscellaneous malignant causes. Histological or cytological confirmation of the diagnosis was obtained in 47 patients (63 per cent). In the remaining 28 patients the diagnosis was based on clinical and radiological findings, and follow-up gave no doubt concerning the diagnosis. The majority of patients had treatment before percutaneous stenting (*Table 1*). Eighteen patients had cholangitis before the percutaneous procedure. The serum bilirubin concentration was measured before stent placement in 67 patients and the median value was 185 (range 29–566) μmol/l (normal range 4–14 μmol/l).

All percutaneous transhepatic biliary drainage procedures were performed under ultrasonographic and fluoroscopic guidance. Broad-spectrum antibiotics were used during the 12 h before and after each procedure. All stents had a diameter of 1 cm; the length varied from 3·5 to 10·5 cm. Balloon dilatation was performed before stent insertion in the first five patients. This was subsequently abandoned as the prostheses continued to expand for a few days after placement. Plain abdominal radiography confirmed the position and degree of expansion of the stents 1–14 days after insertion.

The effect on jaundice, complications and follow-up were recorded for all patients. Early complications were those occurring within 30 days of stent placement. Cholangitis was defined as fever >38°C in the absence of other explanations. Bleeding was assumed after a reduction in the haemoglobin level $\geq 0{\cdot}5$ mmol Fe^{2+} per litre in the absence of other explanations. The serum bilirubin concentration was recorded approximately 1 month after stent placement. The patency period of the prosthesis was taken as the interval between its insertion and the occurrence of biliary obstruction, as defined by clinical symptoms, and ultrasonographic and cholangiographic findings.

Table 1 *Previous therapy in 75 patients treated by percutaneous Wallstent endoprosthesis insertion*

Failed endoscopic attempt	50
Failed endoscopic replacement	12
Previous percutaneous endoprosthesis	1
Palliative biliary bypass	5
Whipple's procedure	1
Cholecystectomy	1
Gastroenterostomy	5
External radiotherapy	5

Results

Endoprosthesis insertion (*Figure 1*) was successful and uneventful in all patients. Stent expansion to >80 per cent of the maximal diameter was seen in all cases. Pre-existing cholangitis resolved in all but two patients. Serum bilirubin concentration after stent insertion was measured in 47 patients, and showed a decrease in all, with a level of less than twice the upper limit of normal in 21 patients after 30 days.

Early complications occurred in 16 patients (21 per cent); they were related to the stent in five (7 per cent) and serious in six (8 per cent) (septicaemia, four; pleural empyema, one; reobstruction, one). Seven patients had cholangitis, including two with pre-existing cholangitis. Four of these seven had septicaemia but all recovered following antibiotic administration. In four patients bleeding of the transhepatic tract was noticed during catheter manipulation, and controlled by leaving the drainage catheter in place for 2 weeks after stent insertion. Bleeding, bile leakage along the catheter and catheter dislocation occurred in one patient each and were treated conservatively. A debilitated patient with a transpleural catheter developed pleural empyema; no therapy was performed as the patient was terminally ill. Reobstruction due to angling of the stent occurred in one patient 21 days after insertion.

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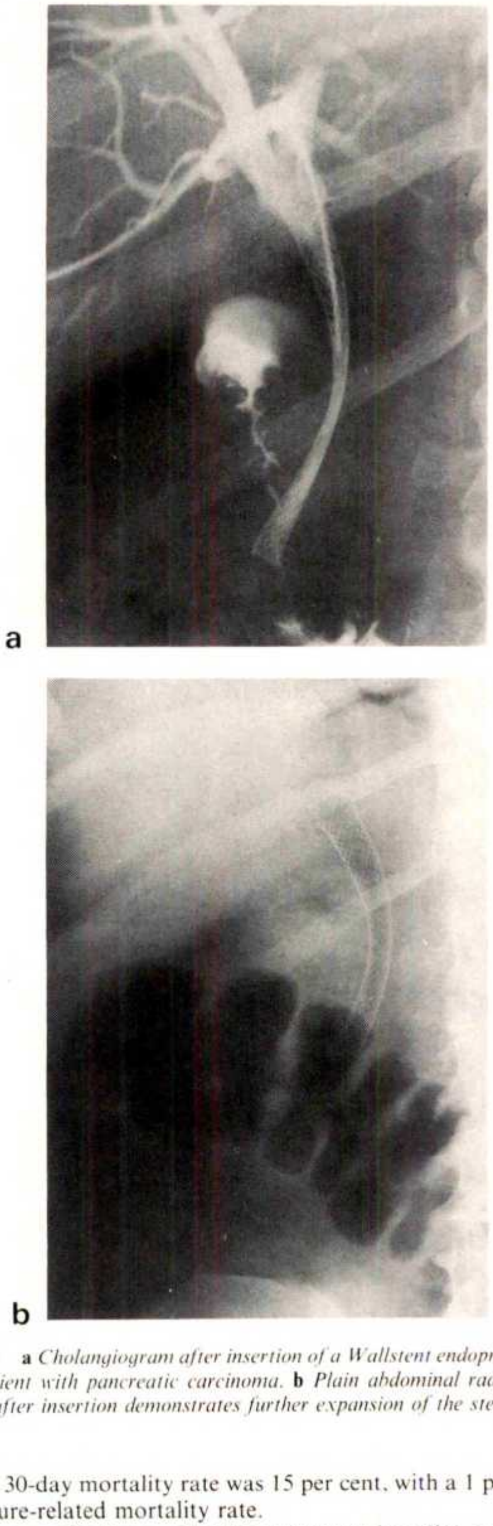

Figure 1 **a** *Cholangiogram after insertion of a Wallstent endoprosthesis in a patient with pancreatic carcinoma.* **b** *Plain abdominal radiograph 4 days after insertion demonstrates further expansion of the stent*

The 30-day mortality rate was 15 per cent, with a 1 per cent procedure-related mortality rate.

Late complications, other than recurrent jaundice, occurred in two patients. One patient developed a pressure ulcer of the duodenum opposite the stent and another had melaena at 45 days that was attributed to the prosthesis because no other cause could be found. Gastroenterostomy was necessary in two patients.

Recurrent jaundice due to stent obstruction occurred in four patients after 21, 127, 176 and 341 days. Tumour ingrowth caused reobstruction in one patient and angulation of the stent caused recurrent jaundice in another. The first patient was treated by catheter drainage, the second by proximal lengthening of the stent. There was clinical suspicion of reobstruction in two terminally ill patients, but no definitive cause was established.

Ten patients remain alive after a median follow-up of 65 (range 31–383) days, with no recurrence of obstruction so far. The other 65 patients died, with a median survival of 87 (range 6–365) days after stent placement. The four patients with reobstruction were in this group.

Discussion

Curative surgery is often not feasible in patients with malignant distal biliary obstruction. Palliative biliary bypass may be performed but non-surgical drainage by stent insertion has proved an important alternative and provides better results than biliary surgery in many institutions[4–7]. Efforts have been made to design an endoprosthesis that is easy to insert and remains patent until death. The major disadvantage of the plastic stents currently available is reobstruction by sludge. Increase of stent diameter might prolong patency but is limited by several factors, such as more difficult manipulation and the possibility of more complications. The design of the self-expandable Wallstent endoprosthesis, with its small delivery catheter, large inner diameter, relatively small surface area and fixation against the wall, seems advantageous in theory, but trial results are required.

Before comparing the present study with others (especially endoscopic) on biliary stenting, differences in study populations should be considered. The majority of patients in the present study had one or more failed endoscopic attempts. This increases the risk of early complications, especially cholangitis, and this patient group is probably more difficult to treat, as one method has already failed.

Early complications in the present series, predominantly cholangitis, occurred in 21 per cent of patients, a rate comparable to that seen with plastic stents[7–11]. The majority of the early complications were caused by the initial catheter drainage and most of these patients had a previous failed endoscopic attempt, thus increasing the risk of cholangitis. Most complications were minor and other studies of the Wallstent endoprosthesis have reported a wide range of early complications[2,12–14].

Reobstruction of plastic stents in malignant distal stricture occurs in approximately 20–40 per cent of cases after 3–5 months[4,5,7,10,11,15] and therefore the rate (5 per cent) associated with the Wallstent endoprosthesis in the present series compares favourably. Blockage by sludge, the major problem in biliary stenting, has become a rare cause of reobstruction[2,12–14,16–19]. Tumour overgrowth seldom causes reobstruction when stents of an adequate length are used. Tumour ingrowth through the mesh of the stent occurs but, since the inner stent diameter is large and survival short, stent obstruction will remain a relatively rare event.

Besides its expanding force the Wallstent prosthesis has a straightening force; this may result in the stent not retaining the form of the bile duct, with subsequent occlusion of the proximal end of the device by the bile duct wall, as occurred in one patient in the present study. This problem can be treated by proximal lengthening of the stent and prevented by using longer stents initially. Reintervention is more easily performed than with plastic prostheses, because another stent or catheter can be placed through the lumen, without the need for stent removal.

The use of the Wallstent endoprosthesis increases the cost of the procedure, and this must be weighed against the reduction in the rate of reobstruction and consequent decrease in the costs of reintervention and rehospitalization[20].

Percutaneous insertion of the Wallstent endoprosthesis to establish definitive biliary drainage without recurrence of jaundice by reobstruction was accomplished in most patients in this study.

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Palliation of biliary obstruction in patients with advanced breast cancer using endoscopic stents

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Endoscopic insertion of a biliary endoprosthesis was successful in eight patients with extrahepatic biliary obstruction caused by breast cancer metastases. The serum bilirubin level was significantly reduced in seven patients and in four this was accompanied by marked symptomatic improvement. Endoprostheses required replacement after a median of 8 (range 3–127) weeks. Two patients responding to systemic anticancer therapy survived 27 and 43 months. Endoscopically placed stents offer effective palliation of extrahepatic biliary obstruction caused by metastatic breast cancer and long-term survival may be possible.

Malignant obstruction of the extrahepatic bile ducts may result from metastatic cancer to the area of the pancreatic head and porta hepatis. This produces distressing symptoms of jaundice, pruritis, nausea and anorexia.

Palliation of extrahepatic biliary obstruction can be achieved surgically, but recent attention has focused on non-operative methods. The development of endoscopic insertion of endoprostheses allows palliation with a short hospital stay and low morbidity and mortality rates[1,2]. In a series of 221 patients with pancreatic cancer, endoscopic management was successful in 90 per cent and there was a procedure-related mortality rate of only 2 per cent[3]. Similar results have been obtained in this institution[4]. Application of the technique to eight patients with breast cancer is described.

Patients and methods

Of 140 patients referred for endoscopic management of malignant extrahepatic biliary obstruction between June 1987 and November 1990, eight women presented with metastatic breast cancer obstructing the distal common hepatic duct or common bile duct (CBD). The median age was 50 (range 40–63) years and all patients were jaundiced at presentation with a serum bilirubin level $\geqslant 90$ mmol/l. All had multiple sites of tumour spread at the time of the initial procedure, including liver metastases in five patients. Extrahepatic biliary obstruction was demonstrated by ultrasonography in each patient.

Two patients had previously been treated for biliary obstruction. In one, cholecystoenterostomy had produced no improvement; percutaneous biliary drainage and chemotherapy had been given with no significant benefit. At endoscopic retrograde cholangiopancreatography (ERCP) the stricture was seen to be proximal to the surgical bypass. The second patient had achieved complete remission of a metastasis to the pancreatic head following chemotherapy 10 months previously and presented this time with further obstruction.

Insertion of an endoprosthesis was attempted at the time of diagnostic ERCP using a standard technique[3]. A small sphincterotomy was made to facilitate access to the CBD. Most initial procedures were performed using an Olympus JF1T10 side-viewing duodenoscope (Keymed, Southend-on-Sea, UK) with a 2·8-mm diameter instrument channel, allowing the insertion of a 7-Fr prosthesis. Replacement of prostheses was usually undertaken with an Olympus TJF10 endoscope with a 4·2-mm channel allowing passage of a 12-Fr stent. Straight prostheses with side flaps to prevent migration were used.

Results

Prostheses were successfully placed at the time of initial endoscopy in seven patients and by a combined endoscopic and percutaneous approach in one. Two patients suffered complications: minor haemorrhage that did not require transfusion and transient antibiotic-related renal failure.

One patient died 5 days after the procedure from pulmonary embolism. The other seven achieved successful drainage, defined as a 50 per cent fall in serum bilirubin level or relief of jaundice within 30 days. Six patients required stent replacement after a median of 8 (range 3–127) weeks (*Table 1*). Occlusion of the endoprosthesis was usually heralded by jaundice and cholangitis.

Six patients improved symptomatically; four of these showed marked improvement and returned to full activity. Seven patients died at 5 days, 5, 11, 19, 31 and 31 weeks, and 43 months after the initial procedure. One patient remained alive at 27 months. The two longest survivors showed prolonged responses to hormone treatment. Neither had initial liver metastases. One patient remained stable on megestrol acetate for 18 months and the other died at 43 months after responding to tamoxifen and megestrol acetate therapy.

Discussion

Malignant extrahepatic biliary obstruction carries a poor prognosis especially if caused by pancreatic cancer, where the median survival after palliative treatment[1,5] is approximately 4 months. In patients with metastatic extrahepatic biliary obstruction in the presence of widely disseminated disease the outlook is also poor; in one study[6] eight of 12 patients died within 2 months.

In a series of seven patients with breast cancer treated by various non-endoscopic means[7], a similar success rate for relief of obstruction and comparable survival rate to those in the present study were observed, but only three patients had other sites of metastatic disease. It was concluded that hepatic metastases precluded significant palliation. In the present study all eight patients had breast cancer metastases at multiple sites; despite this, only two failed to improve symptomatically and six survived longer than 2 months.

The major complication of the procedure was occlusion of the endoprosthesis. Replacement was required after a median of 8 weeks and was often undertaken as an outpatient procedure.

Extrahepatic biliary obstruction caused by metastatic breast cancer can be effectively palliated by endoscopic insertion of a stent despite the presence of widespread metastases. Prolonged survival may be seen in patients responding to systemic anticancer treatment.

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Table 1 *Endoscopic insertion of biliary stents in patients with metastatic breast cancer*

Patient no.	Age (years)	Stent no.	Bilirubin level (μmol/l) Before	Bilirubin level (μmol/l) After	Duration of patency (days)	Patient survival*
1	58	1	90	23	49	
		2	41	19	30	Died after 11 weeks
2	48	1	125	41	28	
		2	63	15	42	Died after 19 weeks
3	63	1	n.k.†	n.k.†	56	
		2	18	15	285	
		3	33	16	133	
		4	32	18	200	
		5	n.k.	n.k.	58	
		6	n.k.	n.k.	39	
		7	n.k.	n.k.	60	Alive after 27 months
4	46	1	277	31	26	
		2	67	10	141	
		3	9	8	50	Died after 31 weeks
5	40	1	249	387	5	Died after 5 days
6	44	1	205	36	22	
		2	59	16	35	
		3	133	13	61	
		4	104	19	99	Died after 31 weeks
7	56	1	289‡	7	49	
		2	41	n.k.	63	
		3	29	7	182	
		4	4	6	887	
		5	5	6	124	Died after 43 months
8	52	1	378	120	28	Died after 5 weeks

*Survival after the initial procedure; †clearance of marked jaundice was observed after first endoprosthesis insertion; ‡bilirubin level before initial percutaneous drainage. n.k., Not known

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Role of early and extensive surgery in the treatment of severe necrotizing soft tissue infection

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Forty-two patients with necrotizing soft tissue infection are reviewed. Bacterial culture revealed between two and seven types of micro-organism in each patient. All patients were treated with radical surgical debridement and a combination of antibiotics. In 30 patients, early diagnosis and treatment resulted in only two deaths. Delayed surgical intervention in 12 patients transferred from outside hospitals was followed by nine deaths. Predisposing factors and site of infection did not affect outcome. Of 26 patients with systemic manifestations of sepsis, 16 survivors responded well to initial surgical debridement.

The mortality rate of patients with necrotizing soft tissue infection is high: 30–60 per cent[1–5]. The terminology used for these infections is related to the kind of pathogen, the tissues involved and the presence or absence of gas in the tissues, e.g. necrotizing fasciitis, streptococcal gangrene, synergistic gangrene, and clostridial or non-clostridial myonecrosis. Necrotizing soft tissue infection is usually a superimposed process in patients with impaired humoral and cellular immunity resulting from previous inflammatory conditions or other factors such as diabetes or alcoholism.

This report describes the details of 42 patients with soft tissue necrotizing infection treated over a 12-year period.

Patients and methods

The 42 patients comprised 28 men and 14 women with a mean age of 55·2 years. Causative mechanisms and predisposing factors were identified on admission, with an evaluation of the extent and severity of tissue involvement. Resuscitation was accomplished within 4–6 h. Fluid from involved tissues was collected for bacteriological analysis and a combination of antibiotics administered.

Under general anaesthesia, extensive radical debridement and resection of all involved tissues was performed. The size of potential defects or cosmetic considerations were not immediate concerns.

Results

The most frequent locations of infection were the abdominal wall (11 patients), the lower extremities (ten) and the perineum (six); both the perineum and hypogastrium were involved in six patients (*Table 1*). Of the six patients with necrosis of the perineum alone, four had Fournier's gangrene; four patients required a diverting colostomy. In three of these patients extension into retroperitoneal tissues was found during surgery. The type of infection varied as shown in *Table 1*. Necrotizing fasciitis was the most frequent manifestation (15 patients). The infections were all polymicrobial, yielding from two to seven (mean 3·5) types of micro-organism per patient. Ten patients had mixed aerobic and anaerobic flora.

The nature of the necrosis and type of surgery in patients with postoperative infection are shown in *Table 2*; all 11 patients had only local signs. A pre-existing neglected purulent process was present in 17 patients, including seven with an intra-abdominal infection, eight with a perineal abscess and two with neglected ischaemic necrosis of the lower limb. In 12 patients predisposing factors such as diabetes (five), immunosuppression (two), alcoholism (two) and multiple trauma (three) were present. Despite the contribution to the

Table 1 *Location of necrosis, type of infection and micro-organisms isolated in 42 patients*

	No. of patients
Location of necrosis	
Abdominal wall	11
Perineum alone	6
Perineum and hypogastrium	6
Upper extremities	6
Lower extremities	10
Shoulder	1
Face	1
Chest wall	1
Type of infection	
Necrotizing fasciitis	15
Clostridial myonecrosis	11
Synergistic gangrene	8
Non-clostridial myonecrosis	4
Streptococcal gangrene	4
Micro-organisms isolated	
Clostridia	23
Gram-negative aerobic bacteria	35
Gram-positive cocci	29
Fungi	2
Staphylococcus aureus	13

Table 2 *Nature of necrosis and type of surgery in 11 patients with postoperative infection*

	No. of patients
Nature of necrosis	
Fasciitis	6
Myonecrosis	4
Synergistic gangrene	1
Type of surgery	
Colonic surgery	2
Appendicectomy	1
Gastrectomy	1
Biliary surgery	1
Prostatectomy	1
Nephrectomy	1
Hysterectomy	1
Bone surgery	1
Tracheostomy	1
Vascular	1

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Table 3 *Organ failure due to sepsis in 18 patients*

	No. of patients
Adult respiratory distress syndrome	15
Septic shock	6
Renal failure	4
Stress ulceration	3
Liver dysfunction	2
Myocardiopathy	2
Coagulopathy	2

development of necrosis, these conditions did not adversely affect outcome and none of these patients died.

Organ failure occurred in 18 patients and was present on admission or developed as a result of sepsis (*Table 3*). The patients required between two and seven (mean 3·5) surgical debridements during hospitalization, excluding procedures required for reconstruction.

There were 11 deaths. Of 12 patients in whom surgical debridement was delayed because of transfer from an outside hospital, nine died. Of 30 patients who underwent radical surgery within the first 24 h, there were only two deaths. Two patients with necrosis of the retroperitoneal tissues survived. Sixteen patients had only local signs of infection and 26 had systemic manifestations of sepsis. In the group with local signs, only one patient died; in the other group, the ten patients who died continued to have systemic manifestations of sepsis after initial surgery. Patients who responded favourably to the initial debridement did well.

Discussion

Severe necrotizing soft tissue infections are known to be polymicrobial. The most severe cases are those in which mixed aerobic and anaerobic flora are found[6]. Necrotizing infections of the trunk (mainly the lower abdomen and perineum) are frequently the result of a neglected postoperative complication or of trauma[3,4]. If the extremities are involved, it is usually the result of trauma or needle puncture and extravasation of drugs.

Predisposing factors include diabetes, alcoholism and immunosuppression (malignancy or chemotherapy). Early treatment in these patients had a favourable outcome. A pre-existing neglected focus could be considered as another predisposing factor. In 17 patients, neglected perineal abscesses and intra-abdominal infections existed before the necrotizing infection, and in four of these patients the infections arose from badly or inadequately treated postoperative complications.

The patients in this series can be divided retrospectively into two groups according to the time of treatment. In previous studies the authors stated that prompt and aggressive debridement remains the cornerstone of management[5]. Radical surgical debridement and antibiotics are of no value if the necrotic process has already extended[7,8]. In 12 patients in whom surgery was delayed there were nine deaths. In previous reports[1–5], the mortality rate ranged from 30 to 60 per cent. The difference in mortality rates does not represent the severity of these infections but rather the difference and timing of the methods of treatment.

Woodburn *et al.*[9] reported five fatal cases of retroperitoneal necrotizing fasciitis. In the present series, there were three patients with sepsis of the perineum extending to the retroperitoneal tissues. Two survived, probably because adequate debridement was possible.

The role of early radical surgical treatment is confirmed as the most important factor affecting outcome. Response to the initial operation might be of prognostic value.

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Early discharge from hospital after open appendicectomy

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A prospective study of 200 consecutive open emergency appendicectomies was carried out. All patients were informed before operation that they would be discharged the following day if possible. The operation was performed through a standard muscle-splitting incision. At the end of the operation the wound was infiltrated with bupivacaine and a diclofenac suppository was given. There were 29 normal, 129 acutely inflamed, six gangrenous and 36 perforated appendices. In all, 147 patients (73·5 per cent) were discharged home within 24 h and reviewed 2 weeks later. Twelve patients had seen their general practitioner, mainly for wound problems (eight) or pain (two). Two others required readmission. Thirty-four patients (23·1 per cent) required no postoperative analgesia; 104 (70·7 per cent) required paracetamol or co-proxamol for $\leqslant 3$ days and nine (6·1 per cent) for >3 days. No patient had a problem directly related to early discharge from hospital. Fifty-three patients (26·5 per cent) were not discharged home early due to peritonitis (36), social reasons (seven), nausea (seven), associated caecal volvulus (one) and pregnancy (two). Early discharge from hospital within 24 h after emergency appendicectomy is safe and has good patient acceptability.

The length of hospital stay for general surgical procedures is steadily declining, although considerable variation exists between one hospital and another[1]. Many elective operations can now be carried out on a day-case basis[2]. With the advent of laparoscopic cholecystectomy and minicholecystectomy, even patients with gallstones can be dealt with on a day-case or short-stay basis[3]. For emergency admissions, however, the decline in hospital stay is less dramatic[4]. It has been claimed that one of the advantages of laparoscopic compared with open appendicectomy is a shorter hospital stay[5,6].

Patients undergoing open appendicectomy often remain in hospital for 3–5 days after operation[1,4,5]. In one study[7], 80 per cent of children with non-perforated appendices were safely discharged within 48 h of operation, although only 3 per cent were allowed home within the first 24 h.

A prospective and consecutive study of emergency open appendicectomy in adults and children has been carried out to assess the safety and feasibility of planned discharge from hospital 24 h after operation.

Patients and methods

All patients were informed before operation of possible discharge home within 24 h provided their clinical condition was satisfactory. A metronidazole suppository was given with the premedication (1 g for adults, 500 mg for children). All patients underwent standard appendicectomy through a muscle-splitting incision under general anaesthesia. Closure of the muscle layers was carried out with an absorbable suture. In the presence of a normal or acutely inflamed appendix, the skin was closed with subcuticular polydioxanone.

At the end of the procedure the wound was infiltrated with 0·25 per cent bupivacaine and a diclofenac suppository given. Intraoperative use of intramuscular opiates and intravenous fluids was left to the discretion of the anaesthetist. Routine use of postoperative intramuscular narcotics and intravenous fluid replacement was avoided whenever possible. Co-proxamol was the analgesic of choice. Patients with gangrenous appendicitis without perforation were given three doses of metronidazole, and those with peritonitis or perforation a therapeutic course of cefuroxime and metronidazole.

No attempt was made to discharge patients with peritonitis or perforation within 24 h. The other patients, with normal, acutely inflamed or gangrenous appendices, who were felt to be suitable for discharge within 24 h, were encouraged to mobilize early. They were allowed oral fluids and diet on full recovery from anaesthesia. Patients were reviewed the next day and allowed home if well.

Patients discharged within 24 h were reviewed 2 weeks later. They were questioned about their general progress, diet and return to normal activity. The nature and duration of oral analgesia required was noted. The wound was examined and any problems such as discharge, bleeding or infection documented. The timing of, and reason for, any visit to their general practitioner (GP) was also noted. Follow-up of patients not discharged within 24 h was left to the discretion of the admitting surgeon.

Results

Of 200 appendicectomies carried out during a 5-month period, 29 appendices (14·5 per cent) were histologically normal, 129 (64·5 per cent) acutely inflamed, six (3·0 per cent) gangrenous and 36 (18·0 per cent) perforated with peritonitis. The operations were performed mainly by surgeons in training: senior house officer, 68; registrar, 127; consultant, five. The patient male:female ratio was 1:1·3.

A total of 147 patients (73·5 per cent) were discharged within 24 h; 53 remained in hospital for >24 h, mainly due to associated peritonitis (*Table 1*). Fifty-five (85 per cent) of 65 children were discharged within 24 h, compared with 92 of 135 adults (68·1 per cent) ($\chi^2 = 6·1$, 1 d.f., $P < 0·02$). This difference was due to the greater likelihood of peritonitis in adults in this series.

Three children and nine adults had seen their GP within the 2-week follow-up period. In ten of the patients this was because of wound problems (discharge, eight; pain, two). Seven of these wounds had a serosanguineous discharge when seen by the GP and two patients were prescribed a course of antibiotics with good resolution. One patient had a wound abscess following removal of a gangrenous appendix, and required readmission and drainage. All the wound problems developed 7–10 days after operation.

Readmission was required in four of the 200 patients. Two of these had been discharged within 24 h; one was the patient with a wound abscess and the other was readmitted with pyrexia and malaise with a suspected pelvic abscess. Examination under anaesthesia and pelvic ultrasonography did not confirm the abscess, and the patient's symptoms improved on conservative

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Table 1 *Reason for failure to discharge 53 patients from hospital within 24 h*

	No. of patients
Children (age < 16 years)	
Peritonitis	7
Nausea or vomiting	1
Social reasons	2
Total	10
Adults	
Peritonitis	29
Nausea or vomiting	6
Associated caecal volvulus	1
Pregnancy	2
Social reasons	5
Total	43

treatment. At the original operation the appendix was normal and large mesenteric nodes had been found.

Thirty-four patients (23·1 per cent) required no analgesia at home. Paracetamol or co-proxamol was required in 104 (70·7 per cent) for ≤ 3 days and in nine (6·1 per cent) for > 3 days. Analgesia requirements were generally lower, but not significantly so, in children compared with adults. The median time taken for patients to resume normal activities was 3 (range 2–7) days and the time to return to work or school was 7 (range 5–14) days. The 53 patients who were not discharged within 24 h stayed in hospital for a median of 3 (range 2–8) days.

Discussion

If patients undergoing laparoscopic cholecystectomy, or even minicholecystectomy, can be discharged from hospital within 24 h of operation, the same principles should apply to uncomplicated appendicectomy. The present results confirm that 90 per cent of patients undergoing emergency appendicectomy without evidence of peritonitis can be discharged within 24 h, whether adults or children.

A careful explanation was given to the patients before operation so that they knew early discharge from hospital was a possibility. Most of the patients and their relatives accepted the concept readily. Following discharge, analgesia requirements were minimal, and virtually all patients had resumed normal activity at the time of follow-up.

The commonest problem likely to be encountered after appendicectomy is infection within the wound. The use of prophylactic antibiotics in the presence of minimal wound contamination can reduce the incidence of this complication to low levels[8]. Eight patients in this series probably had wound infection, one requiring readmission to hospital. Even with a postoperative stay of between 3 and 5 days, most wound infections become apparent only after discharge from hospital. All the wound problems in this series occurred 7–10 days after operation. No morbidity was encountered as a result of early discharge from hospital. Reported readmission rates after appendicectomy are surprisingly high[7]. It was encouraging to find that only two of the 147 patients in the present series who were discharged early required readmission. In one of these, the admission was almost certainly due to further pain from mesenteric adenitis.

These results confirm that early discharge from hospital after emergency appendicectomy has good patient acceptability and provides little extra work for GPs. A number of advantages of laparoscopic compared with conventional appendicectomy have been described[5,6]. These include lower morbidity, a shorter hospital stay and a quicker return to normal activity. If trials comparing the two techniques are to be organized, then the conventional limb of the trial should include patients managed as described in this paper.

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Synchronous abdominoperineal resection without transfusion

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Blood loss and hypovolaemic shock affect the immune system significantly, and perioperative blood transfusion has been shown to be associated with a higher rate of tumour recurrence in patients with cancer and increased susceptibility to infectious complications. Data obtained from patients undergoing synchronous abdominoperineal excision of the rectum were analysed to assess whether such surgery is feasible without transfusion. Twenty-two consecutive unselected patients were studied. There were 16 men and six women of median age 66 (range 48–80) years. The tumour stage was Dukes' B in 11 patients and Dukes' C in 11. Six patients were severely obese according to body mass index. Four patients required blood transfusion (1, 1, 2 and 2 units). There was no hospital mortality and all perineal wounds healed primarily with no wound infection. Fifteen patients received radiation therapy 6 weeks after surgery. Abdominoperineal resection with minimal blood transfusion is feasible in unselected patients.

Blood transfusion may be a significant factor affecting the function of the immune system after operation and leading to an increased susceptibility to infection[1,2] and multiple organ failure. In patients with cancer the immunosuppressive action of transfusion may be deleterious. Some have reported increased recurrence and decreased survival rates in patients with colorectal[3] and breast[4] cancer. Blood loss and hypovolaemic shock affect the immune system[5], and hypovolaemic events significantly enhance tumour growth, independent of blood transfusion[6].

Other deleterious effects of transfusion during surgery are related to the potential risk of transmission of human immunodeficiency virus (HIV) 1 or hepatitis B and C viruses.

From 1983 to 1991 a prospective study was carried out to examine the feasibility of performing synchronous combined abdominoperineal excision of the rectum without blood transfusion.

Patients and methods

Between September 1983 and October 1991, 22 consecutive unselected patients (16 men, six women) underwent synchronous combined abdominoperineal excision of the rectum. All patients had rectal cancer located 0–7 cm from the anal verge. The mean age was 65 (median 66; range 48–80) years. The preoperative condition of each patient was assessed using the American Society of Anesthesiologists (ASA) classification[7].

A final decision to perform abdominoperineal resection was made at surgery when low anterior resection could not be performed safely or because of bulky local extension of the tumour. The 22 patients represented 16 per cent of a total of 139 with rectal cancer operated on during the study period. The remaining 117 patients underwent anterior resection of the rectum.

The body mass index (BMI; weight (kg)/height^2 (m^2)) was calculated[8] for each patient.

Complete closure of the pelvic peritoneum was performed by the abdominal operator after careful inspection of the sacral concavity for all remaining bleeding points. The perineal operator sutured the levator ani muscles in the midline, as well as fat and skin. The sacral concavity below the pelvic peritoneum was drained by two 19-Fr suction drains through separate stab wounds. All patients received broad-spectrum antibiotic therapy from the day of surgery, ending on day 4 after operation.

Results

Physical status and pathological staging

Sixteen patients were classified as ASA grade II, four as ASA III and two as ASA IV. Fourteen patients (*Table 1*) were considered to be moderately to severely obese at the time of surgery. Eleven patients had Dukes' B tumours and 11 Dukes' C (C_1 in ten, C_2 in one).

Postoperative complications and mortality

Morbidity was related mainly to intermittent urinary problems in elderly men with prostatic hypertrophy (urinary tract infection, one; retention, six). Primary healing of the perineal wound was obtained in all patients. The mean duration of hospital stay was 19 (median 20; range 10–37) days. One patient had a pulmonary embolus, but there were no other complications and no deaths. At 6 weeks after surgery, 15 patients received pelvic external-beam radiation therapy because of extensive rectal tumour invasion of the anal sphincters. A total dose of 45–50 Gy was administered at a rate of 9–10 Gy per week.

Blood transfusion, hypotensive episodes and drainage volumes

No patient developed intraoperative hypotension and only four received perioperative transfusion. Anaemia, related to the cancer, was the reason for preoperative transfusion in two patients (with haemoglobin levels of 4·8 and 5·0 mmol/l), who both received 2 units packed red cells. The two other patients who underwent transfusion had preoperative haemoglobin levels of 6·2 and 6·0 mmol/l, and a level of 5·5 mmol/l on day 1 after operation. They were admitted to the intensive care unit because they were ASA grade III and had ischaemic heart disease. Both received 1 unit packed red cells as a routine order

Table 1 *Body mass index before operation in 22 patients*

Grade	Body mass index (kg/m^2)	No. of patients
0 (normal)	20·0–24·9	8
I (moderately obese)	25·0–29·9	8
II (severely obese)	30·0–40·0	6

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from the coronary intensive care unit team. The remaining 18 patients, who did not undergo transfusion, had a mean preoperative haemoglobin level of 7·8 (median 8·0; range 6·4–9·0) mmol/l. At discharge the mean level was 7·2 (median 7·4; range 6·2–8·0) mmol/l. Meticulous control of all bleeding points and careful surgical dissection enabled blood loss to be kept to a minimum without increasing the length of surgery. The mean duration of surgery was 270 (median 240; range 200–420) min. The total volume of drainage fluid was recorded for each patient (mean 220 (median 320; range 125–400) ml). The mean duration of perineal drainage was 4 (range 3–5) days. The volume of drainage fluid for the four patients who underwent transfusion was 130, 150, 200 and 260 ml.

Discussion

Synchronous combined abdominoperineal excision of the rectum for tumours located 0–7 cm from the anal verge was the standard operation for most surgeons[9]. Despite current use of sphincter-saving operations, combined excision of the rectum is an important operative treatment for very low tumours[9]. This type of resection leaves a large perineal wound that can be slow to heal if primary closure has been impossible or considered unsafe. The synchronous approach may be more traumatic than other types of rectal excision, because the total surgical trauma is inflicted in a shorter length of time in two surgical areas. Provided the synchronous method is practised under good conditions by fully trained surgeons it is possible to obtain primary healing of the perineal wound. It is also possible to perform an almost bloodless operation and to avoid blood transfusion. Positioning of the patient in the lithotomy–Trendelenburg position with Lloyd-Davies' leg rests offers a satisfactory approach for the abdominal and perineal dissections, even in overweight patients. None of the six severely obese patients (BMI $\geqslant 30\,\mathrm{kg/m^2}$) in this series required transfusion.

Blood transfusion during and after surgery in patients undergoing elective colorectal procedures is followed by infection in 23 per cent of cases[2]. Others have shown that, in patients with various malignancies[3,4], there is a higher rate of tumour recurrence in those who received blood transfusion. These findings are not uniformly observed[10], and a more recent study[5] has shown that the most significant single factor affecting recurrence rate is the number of hypotensive episodes during the operative procedure. Whichever is the most detrimental variable (blood loss, blood transfusion, hypotensive episodes, or all three), the surgeon must try to avoid all of them.

There are theoretical potential risks of infecting the patient with HIV-1 or hepatitis B and C viruses transmitted by blood transfusion. Such a risk should be sufficient to stimulate surgeons to perform bloodless operations.

These results demonstrate that extensive abdominoperineal resection with minimal transfusion can be performed in unselected patients with low rectal tumours.

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Imipenem prophylaxis in elective colorectal surgery

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In a randomized controlled study of 411 patients undergoing elective colorectal surgery, the efficacy and safety of two different regimens of imipenem were compared with those of a control regimen of cefuroxime plus metronidazole. Surgical infections occurred in 92 (26·4 per cent) of 349 evaluable patients. There were no major differences between the three treatment groups. It is concluded that imipenem is as effective as cefuroxime plus metronidazole in the prevention of sepsis after elective colorectal procedures.

The need to provide antibacterial prophylaxis against aerobic and anaerobic organisms in patients undergoing elective colorectal surgery is well established. Of the methods available, the use of perioperative systemic antibiotics combined with mechanical bowel preparation is widely accepted, particularly in the UK.

The development of carbapenem antibiotics with their extremely broad spectrum of antimicrobial activity provides the opportunity of using a single agent in a variety of situations where combination therapy would otherwise be indicated[1]. This study investigated the use of the antibiotic imipenem for perioperative prophylaxis in elective colorectal surgery, and compared it with the widely used combination of cefuroxime plus metronidazole given over a 24-h period. In addition to a course of imipenem given for a similar perioperative period, a short-course regimen of this drug was also investigated in a three-way randomized controlled study.

Patients and methods

Consecutive patients over the age of 18 years undergoing elective colorectal surgery were deemed eligible for entry into the study, provided that they were not pregnant and had no known allergy to any study drug, no concomitant infection, serious comorbidity or inflammatory bowel disease. Patients who had been treated with antibiotics in the preceding 72 h or who had received steroids, antineoplastic agents or radiotherapy before surgery were also excluded. The study was approved by the local hospital ethics committees.

After giving informed consent, patients were randomly allocated to one of three perioperative regimens. Group 1 received imipenem 1 g at induction of anaesthesia with a single further dose of imipenem 1 g at 3 h after surgery. Group 2 received imipenem 1 g at induction of anaesthesia with a subsequent dose of imipenem 1 g at 3 h after operation and a further two doses of imipenem 500 mg at 8 and 16 h. Group 3 received cefuroxime 1·5 g plus metronidazole 500 mg at induction of anaesthesia and further doses of cefuroxime 0·75 g plus metronidazole 500 mg at 8 and 16 h after surgery. All antibiotics were given intravenously.

A complete medical history was taken and an assessment of nutritional status recorded. Criteria used in this assessment were[2]: weight outside the range 90–110 per cent of ideal for height; upper-arm muscle circumference and/or forearm circumference <85 per cent of normal; grip strength <85 per cent of normal; and serum albumin level <32 g/l.

Variables recorded during the operation included duration of the procedure, residual faecal load in the bowel and an assessment of faecal contamination of the peritoneum. The use of antiseptic lavage was left to the discretion of the operating surgeon. Peritoneal and wound swabs were taken for aerobic and anaerobic culture. All susceptibility testing was conducted using disc diffusion methods.

Patients were examined daily for at least 1 week for signs and symptoms of infection. Because of the insidious nature of some postoperative infections, patients were re-examined 6–8 weeks after surgery. When an infection was suspected, appropriate specimens were taken for microbiological culture. Infections were considered to be directly related to surgery if a purulent discharge from the wound occurred, a positive bacteriological culture was obtained, or a deep abscess developed at the site of operation. Similarly, the presence of intra-abdominal abscess, septicaemia or peritonitis was recorded. Wound or anastomotic dehiscence was not considered to be a primary infectious complication: infection resulting from such dehiscence was not therefore counted in the analysis. Other infectious morbidity not so directly related to surgery was also documented.

In the design of the study it was decided that halving the postoperative infection rate would be clinically significant; this premise determined the size of the trial. To detect a reduction of the infection rate from 30 to 15 per cent, 118 patients were required in each treatment group ($\alpha = 0·05$, $\beta = 0·2$).

Comparison of proportions between groups was performed using the χ^2 test. Other comparisons were made through the 95 per cent confidence interval (c.i.).

Results

A total of 411 patients were entered into the study. Of these, 349 were ultimately deemed to be fully evaluable. Reasons why patients could not be evaluated were the finding of non-colonic pathology at laparotomy (27 cases), discovery of established sepsis (13), incorrect allocation (eight), administration of additional perioperative antibiotics (seven), delayed wound closure (four), reoperation required within 72 h (three) and death within 48 h (two).

Patients in the three treatment groups were well matched for age, sex, intraoperative diagnosis and preoperative

Table 1 *Demographic data*

	Group 1	Group 2	Group 3
Patients entered	135	138	138
Patients evaluable	113	114	122
Male*	62 (54·9)	49 (43·0)	65 (53·3)
Mean(s.d.) age (years)	66·0(11·5)	67·7(11·7)	69·0(11·4)
Mean(s.d.) length of operation (min)	92·4(34·9)	91·0(39·1)	94·4(41·5)
Faecal contamination*			
None	1 (0·9)	0 (0)	1 (0·8)
Minimal	105 (92·9)	105 (92·1)	113 (92·6)
Moderate	6 (5·3)	7 (6·1)	5 (4·1)
Severe	0 (0)	2 (1·8)	2 (1·6)
Faecal residue*			
None	18 (15·9)	24 (21·1)	13 (10·6)
Little	81 (71·0)	76 (66·7)	90 (73·8)
Moderate	12 (10·6)	6 (5·3)	12 (9·8)
Abundant	1 (0·9)	8 (7·0)	6 (4·9)
Patients with one or more indicators of poor nutritional status	27	38	33

*Values in parentheses are percentages

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Table 2 *Intraoperative diagnoses and surgical procedures in evaluable patients*

	Group 1 ($n = 113$)	Group 2 ($n = 114$)	Group 3 ($n = 122$)
Intraoperative diagnosis			
Colorectal cancer	86	90	91
Diverticular disease	7	6	12
Colostomy closure and repair	9	10	10
Benign colonic tumour	3	4	2
Other	8	4	7
Surgical procedure			
Right hemicolectomy	26	12	19
Left hemicolectomy	6	9	5
Sigmoid resection	21	18	30
High anterior resection	10	14	12
Low anterior resection	13	15	6
Abdominoperineal resection	17	13	15
Colostomy	2	9	10
Colostomy closure	4	5	2
Hartmann's procedure	3	5	4
Hartmann's closure	4	5	7
Subtotal colectomy	2	6	7
Total colectomy	4	1	3
Other	1	2	2

Table 3 *Clinical outcome of prophylaxis*

Infection	Group 1 ($n = 113$)	Group 2 ($n = 114$)	Group 3 ($n = 122$)
None	54 (47·8)	63 (55·3)	57 (46·7)
Non-surgical	26 (23·0)	28 (24·6)	29 (23·8)
Surgical	22 (19·5)	12 (10·5)	18 (14·8)
Both surgical and non-surgical	11 (9·7)	11 (9·6)	18 (14·8)

Values in parentheses are percentages

Table 4 *Surgical infections occurring in evaluable patients*

Infectious complication	Group 1	Group 2	Group 3
Abdominal wound infection	23	22	17
Perineal wound infection	7	3	6
Intrapelvic abscess	2	2	4
Intra-abdominal abscess	2	1	3
Discharging drain	8	8	10
Peritonitis	0	1	1
Septicaemia	2	2	6
Total	44	39	47

Some patients suffered more than one type of infectious complication

Table 5 *Type and number of bacterial isolates in evaluable patients after surgery*

Organism	Group 1	Group 2	Group 3
Escherichia coli	22	12	16
Other coliforms	11	12	10 (1)
Other Gram-negative aerobes	3	2	8 (2)
Staphylococcus aureus	1	8	4
Other staphylococci	5	6	6
Streptococcus spp.	1	1	2
Enterococcus spp.	5	8	7
Bacteroides spp.	10	14	3
Other anaerobes	8	10	5

Values in parentheses are numbers of isolates resistant to allocated treatment

nutritional status (*Tables 1* and *2*). Other possible prognostic factors, such as faecal contamination, faecal residue in the bowel and experience of the surgeon, were also recorded and were similar for the three groups. There were minor differences in the type of surgical procedure performed, with a preponderance of right hemicolectomy in group 1 and comparatively few low anterior resections in group 3 (*Table 2*). These differences were not significant and did not affect the results of the study. Patients who received antiseptic lavage were matched for age, sex and diagnosis with those not receiving lavage. As no differences were found in the incidence of postoperative complications between these groups, this factor was not considered further.

After surgery, 54 patients (47·8 per cent (95 per cent c.i. 38·6–57·0 per cent)) in group 1, 63 patients (55·3 per cent (95 per cent c.i. 46·1–64·4 per cent)) in group 2 and 57 patients (46·7 per cent (95 per cent c.i. 37·9–55·6 per cent)) in group 3 were free from infection (*Table 3*). The remainder had either infections related to surgery, non-surgical infections, or both. There were no significant differences between the three treatment regimens in their ability to prevent infection (*Table 4*), either overall ($\chi^2 = 2{\cdot}01$, 2 d.f., $P > 0{\cdot}05$) or for infections clearly related to surgery ($\chi^2 = 3{\cdot}34$, 2 d.f., $P > 0{\cdot}05$).

The duration of hospital stay for patients in each treatment group was recorded. No differences in median (interquartile range) stay were found: group 1, 13 (10–16) days; group 2, 13 (10–17) days; and group 3, 13 (10–18) days.

The pathogens isolated after surgery from the clearly surgical infections are shown in *Table 5*. These data include all the significant bacterial isolates grown from the first specimen from each site, but not isolates from the same site obtained on subsequent days. Similar numbers of bacteria were isolated from each treatment group. There was, however, a significantly different distribution of aerobic and anaerobic isolates detected between the three groups ($\chi^2 = 7{\cdot}19$, 2 d.f., $P < 0{\cdot}05$). Anaerobes were cultured from 12, 15 and six patients in groups 1, 2 and 3, respectively, although these differences were not statistically significant ($\chi^2 = 4{\cdot}94$, 2 d.f., $P > 0{\cdot}05$). All isolates from surgical infection sites in groups 1 and 2 were susceptible to imipenem. Three isolates (two *Pseudomonas* spp., one *Proteus vulgaris*) in group 3 were found to be resistant to cefuroxime. A number of isolates in each treatment group were not susceptibility tested. The minimum time that elapsed before the isolation of bacteria was 2 days in groups 1 and 3, and 3 days in group 2.

Adverse events thought to be possibly related to the study drug were recorded in two patients in group 1 (phlebitis), five in group 2 (two hypotension, one each of phlebitis, rash and erythema) and three in group 3 (diarrhoea). All patients recovered spontaneously from these events.

Discussion

Patients in the control group receiving cefuroxime plus metronidazole (group 3) suffered a surgical 'sepsis rate' of 29·5 per cent. Given this, the power of the study to detect a reduction of 15 per cent was 80 per cent at a significance level of 5 per cent. It is clear from this that both regimens of imipenem provided equivalent protection to that afforded by the triple-dose therapy of cefuroxime plus metronidazole. It is particularly interesting to see that the efficacy of the short two-dose course of imipenem appeared to be as effective as 24 h of prophylaxis with cefuroxime–metronidazole or imipenem. There were no obvious differences between the two imipenem regimens in the proportion of patients developing a postoperative infection, the type of infection nor the duration of hospital stay. This is further evidence supporting the use of short-course prophylaxis in non-contaminated patients undergoing elective colorectal surgery[3,4].

It must be emphasized, however, that such short-course prophylaxis may not prove optimal if significant contamination should inadvertently occur at operation, or if there is established sepsis already present. In this study care was taken to exclude patients with such established sepsis, and also those with inflammatory bowel disease. Similarly, patients were withdrawn from the study if unsuspected sepsis was discovered at laparotomy. Therefore, despite the encouraging results of this study, caution must be exercised before advocating short-course prophylaxis for all colorectal procedures.

More aerobic isolates were obtained from patients in group 3 than in the imipenem groups (1 and 2). In addition, a greater diversity of anaerobic organisms was isolated from the imipenem groups, even though the proportion of patients who subsequently developed anaerobic infection was similar. The *in vitro* antianaerobic spectra of activity of imipenem and metronidazole are similar with few, if any, isolates being resistant to either drug. On the other hand, imipenem has a broader spectrum of antiaerobic activity than cefuroxime, particularly against *Pseudomonas aeruginosa*, *Enterobacter* spp. and the enterococci. Despite this, the number of isolates in this study resistant to any antibiotic was small. It seems unlikely, therefore, that any differences in the *in vitro* spectra were responsible for the clinical dissimilarity. These apparent differences are more likely to be artefacts caused by the low number of patients with isolates and are probably not of clinical significance.

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Effect of putative phospholipase A_2 inhibitors on acetic acid-induced acute colitis in the rat

Phospholipase activation may play an important role in ulcerative colitis. This hypothesis was tested by evaluating the effect of two non-selective phospholipase (PL) A_2 inhibitors, quinacrine and p-*bromophenacylbromide (pBPB), on acetic acid-induced colitis in the rat. The calcium antagonist verapamil, which may also act as a PLA_2 inhibitor, was also tested. Acute colitis was induced in an isolated colonic segment by instillation of 4 per cent acetic acid for 15 s; this induces a uniform colitis after 4 days. The severity of colitis was evaluated histologically, by measuring myeloperoxidase (MPO) activity and by determining plasma exudation into the lumen of the colon (permeability) with ^{125}I-labelled albumin given intravenously. All three putative PLA_2 inhibitors tested were found to prevent the development of colitis. Intravenous administration of quinacrine 10 mg kg^{-1} at 30 min before instillation of acetic acid resulted in a normal mucosal appearance, normal MPO activity and a significantly reduced increase in plasma exudation into the colon. A similar effect was achieved using verapamil. Intracolonic administration of either quinacrine or pBPB also prevented acetic acid-induced colitis. However, three doses, starting immediately after acetic acid administration and repeated on the first and second days, were needed to achieve this, whereas one dose produced only a partial effect. PLA_2 may play an important role in acetic acid-induced colitis and inhibition of its activity may offer an alternative mode of treatment in ulcerative colitis.*

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The pathogenesis of ulcerative colitis is largely unknown, although oxygen free radicals and products of phospholipase activation have been suggested to play an important role[1–3]. When oxygen free radicals are generated, they initiate a chain reaction in membrane-bound lipids that leads to lipid peroxidation and consequent activation of phospholipase (PL) A_2[4,5]. Furthermore, oxygen free radicals may induce Ca^{2+} influx into cells, which could then activate several calcium-dependent enzymes[6], including PLA_2. Activated PLA_2 acts on the membrane phospholipids to release arachidonic acid, the precursor of several inflammatory mediators[7,8]. Moreover, PLA_2 might be involved in the initiation of a cascade that generates a variety of bioactive and potentially noxious products, including arachidonic acid metabolites, lysophospholipids and platelet-activating factor[9,10]. This suggests that inhibition of this cascade, either by scavenging oxygen free radicals or by inhibiting PLA_2, could be an effective treatment of ulcerative colitis. Several studies have shown that oxygen free radical scavengers are effective in the treatment of experimental acetic acid-induced colitis in the rat[2,11]. Furthermore, the efficacy of one of the most commonly used drugs in ulcerative colitis, 5-aminosalicylic acid, has been considered to be due partly to its antioxidant properties[12,13]. However, there seem to be no data on the potential effect of PLA_2 inhibitors in the treatment of ulcerative colitis.

It has been shown[14] that acetic acid at a concentration of 4 per cent administered for 15 s into an isolated rat colonic segment induces a uniform acute colitis on day 4 after acetic acid instillation, and that the colitis resolves spontaneously after 14 days. In the present study, the same model was used to investigate the therapeutic effect of two PLA_2 inhibitors, quinacrine and *p*-bromophenacylbromide (pBPB), and the calcium antagonist verapamil[15]. These effects were evaluated by changes in colonic morphology, myeloperoxidase (MPO) activity of the same tissue, and plasma exudation into the lumen of the colonic segment.

Materials and methods

Animals

Female Sprague–Dawley rats weighing 230–250 g were purchased (Møllegaard, Ejby, Denmark) and fed on a standard pellet diet with tap water *ad libitum* before and after surgery.

Surgical procedure

The surgical procedure has been described in detail previously[14]. In brief, a midline laparotomy was performed under ether anaesthesia. The caecum, ascending colon and proximal third of the transverse colon were isolated and the ends brought out through two colostomies with an intact blood supply. Gastrointestinal continuity was re-established using an ileocolic anastomosis. The isolated colonic segment was washed several times with warm (37°C) normal saline. Colitis was induced in the isolated colonic segment by instillation of 4 per cent acetic acid solution for 15 s with a volume (8–10 ml) matching that of the segment. At the end of the exposure to acetic acid, the colonic segment was rinsed three times with the same volume of warm normal saline. Control normal rats were surgically prepared in the same manner but received normal saline instead of acetic acid.

Experimental design

After surgical preparation, 96 rats were divided into eight equal groups. Group 1 consisted of control normal rats (surgically prepared without acetic acid administration) and group 2 of control colitis animals (surgically prepared with acetic acid administration). Both control groups were then treated with normal saline. In groups 3–8, rats had colitis induced as in group 2, but were treated with quinacrine 10 mg kg^{-1} intravenously (group 3), quinacrine locally with one dose of 5 mg per rat (5 ml of 1 mg ml^{-1}, group 4) or with three doses (group 5), pBPB locally using one dose of 5 mg per rat (5 ml of 1 mg ml^{-1}, group 6) or three doses (group 7), or verapamil 0·1 mg kg^{-1}

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intravenously (group 8). (Reagents were purchased from Sigma Chemicals, St Louis, Missouri, USA.) Intravenous treatment was given 30 min before acetic acid administration; local treatment was either administered as a single dose immediately after acetic acid instillation or repeated on the first and second days after surgery (three doses).

Histological examination

Six rats from each group were killed on day 4 after operation by an overdose of ether. The isolated segment of colon was divided longitudinally into two parts, one for histological examination and one for measurement of MPO activity. The part for histological examination was fixed in neutral phosphate-buffered 4 per cent formalin. Ten transverse 4–5-μm slices were taken from different sites along the whole length of the isolated colon in each rat. The slices were stained with haematoxylin and eosin, examined using light microscopy and scored in ignorance of the treatment given. A scale was used[14] to determine the extent of inflammatory reaction in the colonic mucosa. Each of the eight measurements estimated was graded from 0 to 3 depending on the severity of changes found (0, none; 1, mild; 2, moderate; 3, severe). The total score for each animal (maximum 24) was calculated. The features assessed were ulceration, mucus cell depletion, crypt abscesses, inflammatory cysts, mucosal atrophy, oedema, inflammatory cell infiltration and vessel dilatation.

Myeloperoxidase activity

The remaining half of the colonic segment was further divided longitudinally into two parts, one for measuring MPO activity, the other for measuring the dry weight:wet weight ratio. MPO activity was determined by a slightly modified method of Grisham *et al.*[16] in which the enzyme catalyses the oxidation of 3,3′,5,5′-tetramethylbenzidine by hydrogen peroxide to yield a blue chromogen with a wavelength maximum at 655 nm. By definition, 1 unit of enzyme activity produced a change in absorbance per minute of 1·0 at 37°C, expressed as units per gram dry weight.

Plasma exudation into the colonic lumen

Increased mucosal permeability for large molecules was estimated by plasma exudation into the lumen of the isolated segment of colon. This served as an index of acetic acid-induced inflammation.

On the fourth day after surgical preparation and the instillation of acetic acid or normal saline, 48 rats were anaesthetized with ether. The body temperature was maintained at 37°C using a heating pad controlled by a rectal thermistor. The right femoral vein and artery were cannulated. The isolated part of the colon was then cannulated through the colostomy apertures using Silastic (Dow Corning, Midland, Michigan, USA) catheters of internal diameter 3 mm. The plasma tracer, ^{125}I-labelled albumin (Isotoplaboratoriene, Kjeller, Norway) in a volume of 0·1 ml (activity 0·4 MBq), was injected intravenously. Blood samples from the femoral artery were taken 15 min after injection of radiolabelled albumin for determination of the plasma tracer concentration. The isolated colonic segment was perfused intermittently (5 ml every 5 min) through the upper colostomy aperture with warm (37°C) Krebs buffer solution for 30 min. The washed-out solution was collected every 5 min from the lower colostomy aperture and each aliquot measured individually in a γ counter. The total radioactivity of the six samples was then calculated. At the end of 30 min the rats were killed by an overdose of ether and the isolated colon resected for measurement of dry weight. Mucosal permeability was expressed as plasma equivalents in microlitres per minute per gram dry weight for the 30-min period.

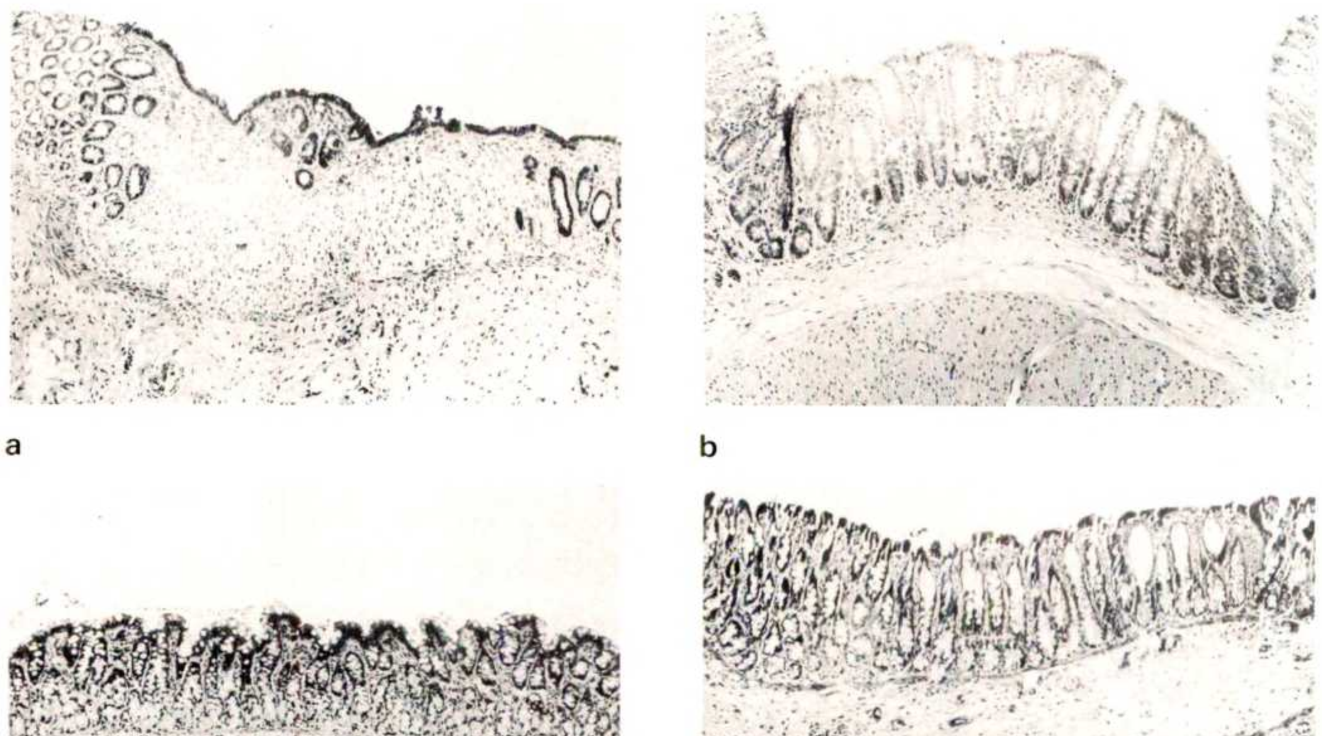

Figure 1 *Photomicrographs showing changes in the colonic mucosa on the fourth day after surgery and acetic acid instillation, except for control normal rats, which received normal saline.* **a** *Control colitis rat. Moderate ulceration, disappearance of glands with mucus cell depletion, cyst formation, moderate inflammatory cell infiltration, oedema and vessel dilatation in the submucosa are visible.* **b** *Control normal rat. Normal mucosa with absence of ulceration and inflammation, substantial mucin production within the glands and slight oedema in the submucosa are seen.* **c** *Rat treated with intravenous quinacrine. Well preserved mucosa with absence of ulceration, minor inflammatory cell infiltration, mucin atrophy and mild oedema in the submucosa are visible.* **d** *Rat treated with intravenous verapamil. Mucosa without ulceration, minor inflammatory cell infiltration, dilated glands with cyst formation, mucin atrophy, mild oedema and moderate vessel dilatation in the submucosa are visible. (All haematoxylin and eosin stain, original magnification ×25)*

Table 1 *Influence of putative phospholipase A_2 inhibitors on histological changes, myeloperoxidase activity and mucosal permeability in the rat colon after acetic acid-induced colitis*

Group	Morphological score	Myeloperoxidase activity (units per g dry weight)	Plasma exudation (μl per min per g dry weight)
Controls			
Normal	1·7(0·3)*	83·8(5·5)‡	0·17(0·02)‡
Colitis	15·7(0·4)§♯	253·8(17·8)	1·43(0·17)
Quinacrine			
Intravenous 10 mg kg^{-1}	3·8(0·8)*	82·6(6·5)‡	0·47(0·05)‡
Locally 3 × 5 mg	5·5(0·4)*§	120·7(16·1)‡	0·59(0·09)†
Locally 1 × 5 mg	7·3(0·4)*§	189·3(18·3)*	1·14(0·15)
p-Bromophenacylbromide			
3 × 5 mg	5·5(0·6)*♯	138·9(18·6)‡	0·52(0·10)†
1 × 5 mg	7·5(0·6)*♯	177·0(21·8)†	0·94(0·16)
Verapamil 0·1 mg kg^{-1}	6·3(0·5)*	98·9(9·6)‡	0·45(0·04)‡

Values are mean(s.e.m.). There were six rats in each group for each measurement. *$P < 0·05$; †$P < 0·01$; ‡$P < 0·001$ (*versus* control colitis group). §Dose-dependent correlation for local treatment with quinacrine: $n = 18$, $r_S = 0·907$, $P < 0·001$; ♯dose-dependent correlation for local treatment with *p*-bromophenacylbromide: $n = 18$, $r_S = 0·886$, $P < 0·001$

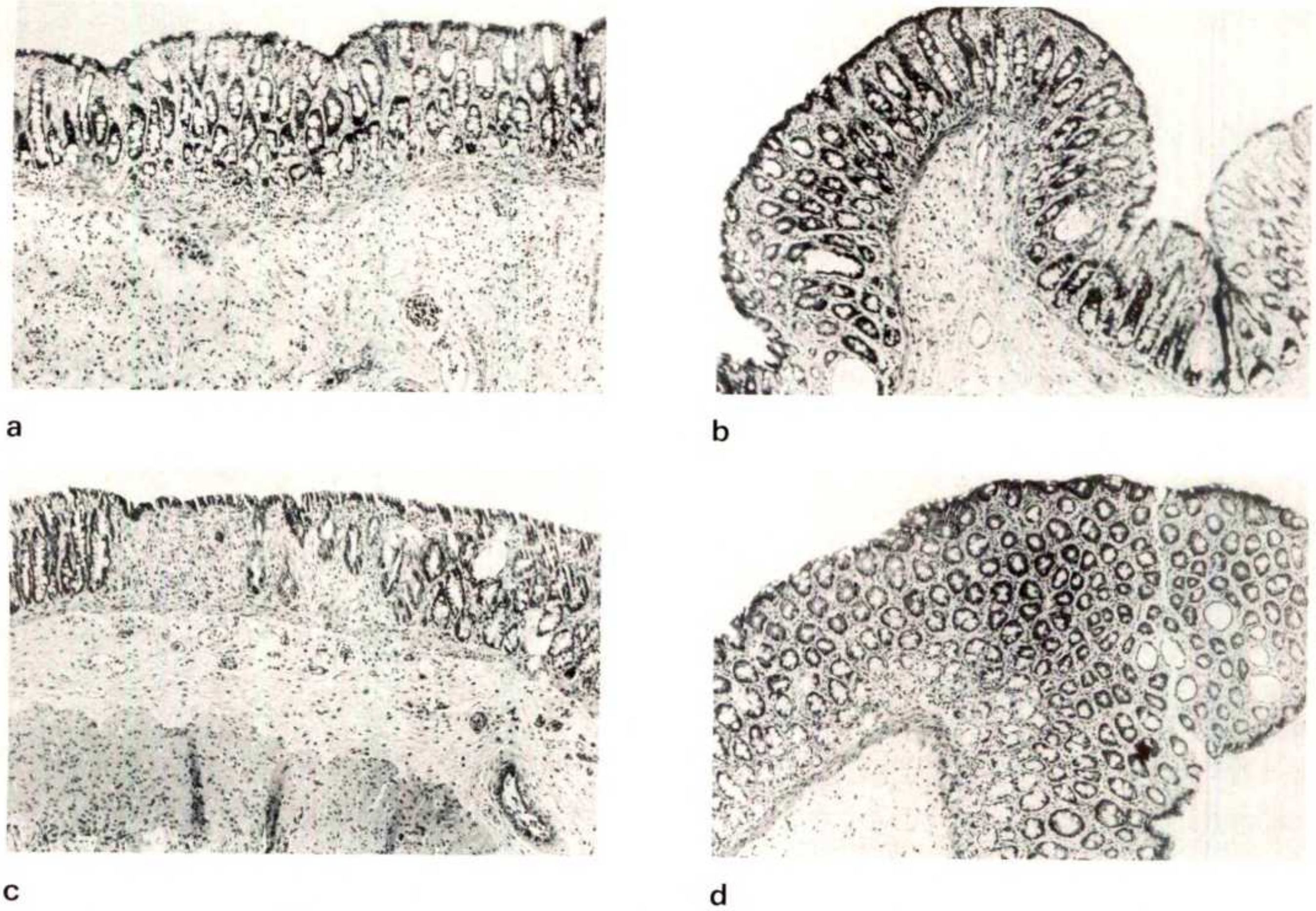

Figure 2 *Photomicrographs showing changes in colonic mucosa on the fourth day after operation and acetic acid instillation.* **a** *Rat treated with one dose of quinacrine locally immediately after acetic acid instillation. Mucosa without ulceration, cyst formation, moderate inflammatory cell infiltration, mild oedema and moderate vessel dilatation in the submucosa are visible.* **b** *Rat treated with quinacrine locally for 3 days. Mucosa without ulceration, dilated glands with cyst formation, simple crypt abscesses, mild inflammatory cell infiltration and mild vessel dilatation are visible.* **c** *Rat treated with one dose of* p-*bromophenacylbromide (pBPB) locally immediately after acetic acid instillation. Mucosa with mild erosion, dilated glands with cyst formation, moderate inflammatory cell infiltration, mild oedema and vessel dilatation in the submucosa are visible.* **d** *Rat treated with pBPB locally for 3 days. Mucosa without ulceration, minor inflammatory cell infiltration, severe cyst formation and minor oedema in the submucosa are visible. (All haematoxylin and eosin stain, original magnification ×25)*

Statistical analysis

The Wilcoxon rank sum test was used for comparison of histological scores. Student's *t* test was used for analysis of MPO activity and plasma exudation. The relationship between morphological score for inflammatory cell infiltration and MPO activity in the colonic tissue was analysed by linear regression. The relationship between the total morphological score and different doses of locally applied treatment was tested using Spearman's rank correlation coefficient. Results are considered significant at $P < 0·05$.

Results

Histopathological examination

Administration of 4 per cent acetic acid into the isolated colonic segment resulted in uniform colitis as evaluated on the fourth day, with mild to moderate signs of ulceration, inflammatory cell infiltration, oedema, crypt abscesses, cysts and dilated vessels and a mean(s.e.m.) morphological score of 15·7(0·4) (*Figure 1a*; *Table 1*). In contrast, control normal rats without acetic acid administration had slight oedema and sometimes dilated vessels, the mean(s.e.m.) score being 1·7(0·3) (*Figure 1b*).

Rats treated with intravenous quinacrine appeared to have an almost normal mucosa with no sign of ulceration, and a significantly lower mean morphological score than control colitis rats (*Table 1; Figure 1c*). Local treatment with one dose of quinacrine produced partial mucosal preservation with no sign of ulceration (*Table 1; Figure 2a*). Repeated local treatment for 3 days further improved mucosal preservation, although this was not significantly different from that seen after intravenous treatment (*Table 1; Figure 2b*). The dose–response relationship for the two local-dose regimens of quinacrine was highly significant. Similar results were achieved after local treatment with pBPB (*Table 1; Figure 2c* and *d*). The dose–response relationship for the two local-dose regimens of pBPB was again highly significant. Intravenous treatment with verapamil gave a similar result to that with intravenous quinacrine (*Figure 1d*).

Myeloperoxidase activity

MPO activity (*Table 1*) was significantly higher on the fourth day after acetic acid administration in control colitis rats than in control normal animals. Treatment with quinacrine, pBPB or verapamil significantly decreased MPO activity compared with the control colitis group. After intravenous treatment with quinacrine or verapamil, MPO activity was completely normal. Local treatment with one dose of quinacrine or pBPB also decreased MPO activity, although the level remained significantly higher than in control normal rats. Local administration of three doses of quinacrine or pBPB further decreased MPO activity to near-normal levels. The morphological score for inflammatory cell infiltration correlated with MPO activity ($n = 48$, $r = 0{\cdot}897$, $P < 0{\cdot}001$).

Plasma exudation into the colonic lumen

On the fourth day after acetic acid administration, plasma exudation into the colon increased in control colitis compared with control normal rats (*Table 1*). Treatment with quinacrine, pBPB or verapamil significantly reduced plasma exudation compared with control colitis animals, although it remained significantly higher than in control normal rats (*Table 1*).

Discussion

These results show a high efficacy of putative PLA_2 inhibitors in preventing the development of acetic acid-induced colitis. Since there is no known specific PLA_2 inhibitor, three drugs reported to inhibit PLA_2 activity in different ways were used. Quinacrine, an antimalarial agent, affects the enzyme–substrate interface, pBPB covalently binds to the active site of PLA_2, and verapamil reduces the intracellular level of calcium, which is necessary for activation of the enzyme[15]. All three agents were found to be effective in preventing the development of colitis, as demonstrated by histological score, MPO activity and plasma exudation into the lumen of the colonic segment.

MPO is an enzyme present in neutrophils and, at much lower concentration, in monocytes and macrophages[17]. The level of MPO activity appears to be directly proportional to the number of neutrophils in the inflamed tissue[18]. Therefore, measurement of MPO activity is a sensitive quantitative assay for acute intestinal inflammation[17,18]. In the present study, the morphological score for inflammatory cell infiltration correlated with MPO activity ($r = 0{\cdot}897$, $P < 0{\cdot}001$).

The colonic epithelium provides a selective barrier to the transmucosal exchange of solutes and fluids. Inflammation could disrupt this barrier and result in increased permeability, which is suggested to be involved in the pathogenesis of inflammatory bowel disease (IBD)[19]. Thus, changes in mucosal permeability could also indicate mucosal injury and inflammation. Since exudation of plasma across the colonic mucosa occurs in IBD, and permeability has been suggested to correlate with the extent of disease[20,21], we believe that measurement of plasma exudation into the colonic lumen could be an appropriate method for evaluation of mucosal injury. This view was supported by the present results, as a dose-related effect was seen on plasma exudation as well as on total morphological score and MPO activity.

Despite the obvious difference in aetiology between experimental acetic acid-induced colitis and human ulcerative colitis, these models may be useful in investigating the pathogenesis of ulcerative colitis and studying the events that occur at the time of inflammation. As in human IBD, the pathogenesis of acetic acid-induced colitis is not fully understood[22]. However, pathological changes present in human ulcerative colitis have also been reported to occur in experimental acetic acid-induced colitis, such as altered vascularization[23], increased mucosal permeability[24] with enhancement of systemic uptake of intestinal bacteria[25], and increased arachidonic acid metabolism[12,26,27]. Arachidonic acid metabolism in acetic acid colitis is similar to that in human IBD[27]. This might imply that, although colitis can be triggered by different stimuli, the same inflammatory mediators are effecting the final response. The acetic acid-induced colitis model may therefore be appropriate for studying the effect of PLA_2 inhibitors. The present experimental system of colitis has two advantages over previously described acetic acid colitis models: it eliminates the influence of luminal factors acting on the colonic mucosa and it is standardized and reproducible[14].

By 4 days after acetic acid administration, MPO activity increased threefold and mucosal plasma exudation into the colonic lumen increased eightfold in rats with colitis compared with control normal animals. The fourth day was chosen as the optimal time to evaluate the effect of PLA_2 inhibitors. The morphological scores of the control normal and control colitis groups in the present study (*Table 1*) were close to previous results[14], confirming the reproducibility of the model.

These results show that both systemic and local administration of PLA_2 inhibitors are effective in preventing acetic acid-induced colitis. However, intravenous administration of quinacrine gave better results than local intracolonic administration. The effect of intracolonic administration was also good, but three repeated doses were needed. This might be due to the amount of quinacrine that remained in the isolated colon and was subsequently absorbed into the colonic mucosa to inhibit the enzyme. On the other hand, the superiority of intravenous administration might be due to the timing of drug delivery, 30 min before acetic acid instillation. This could have led to relatively high concentrations of the drug at the time of acetic acid administration, which inhibited the activated enzymes. The plasma half-life of quinacrine in the rat is not known; however, in humans it is about 1 week and in rabbits about 26 h, which suggests that in the rat it would be several hours[28].

Recent findings indicate that PLA_2 activation plays an important role in mediating ischaemic intestinal injury in rats[5]. It has been suggested that similar mechanisms are at least partly responsible for the mucosal inflammation and injury associated with ulcerative colitis[1,2,11]. Histological analysis of mucosal samples from patients with ulcerative colitis has revealed many similarities with mucosa taken after ischaemia-induced intestinal injury[29]. Such similarities may be due to the activity of oxygen free radicals in both ischaemic injury and intestinal inflammatory disease[30].

One of several mechanisms by which oxygen free radicals may injure the intestinal mucosa is lipid peroxidation[6,30,31]. During peroxidic decomposition of the organelle membrane lipids, the activity of PLA_2 increases[32]. Intestinal ischaemia has been found to be connected with increased levels of PLA_2, decreased activity of lysophospholipase, and an increased ratio of lysophosphatidylcholine to phosphatidylcholine[4,5]. Moreover, the intestinal mucosa could be protected from ischaemic injury by the PLA_2 inhibitor quinacrine[4,5]. In fact, quinacrine has been shown to be more effective in preventing mucosal injury than oxygen radical scavengers[4,5]. Since levels of oxygen free radicals have been reported to increase during active ulcerative colitis, their mode of action may be similar to that noted in ischaemic intestinal injury. Thus, lipid oxidation and PLA_2 activation should be expected. PLA_2 is involved in the generation of bioactive and potentially noxious metabolites, such as arachidonic acid metabolites, lysophospholipids and platelet-activating factor[9,10,33]. These metabolites are all known mediators of inflammatory reaction in ulcerative colitis[3,26,34]. The products of both pathways of arachidonic acid metabolism (the cyclo- and lipo-oxygenase pathways), as well as platelet-activating factor and lysophospholipid, have been detected in inflamed mucosa in human and experimental colitis[3,9,17,33–35]. Inhibitors of these metabolites could, at least partly, reduce mucosal injury in ulcerative colitis[36]. Therefore, the inhibition of PLA_2 could be effective in the treatment of ulcerative colitis. This hypothesis is consistent with current evidence[37] suggesting that the anti-inflammatory effect of corticosteroids, the most effective treatment for ulcerative colitis, may be mediated by induction of the synthesis of a peptide (lipocortin) that inhibits PLA_2. Moreover, the importance of PLA_2 activity in ulcerative colitis is supported by a recent clinical study showing correlation between serum levels of the enzyme and the endoscopically determined severity of disease[38].

In summary, three different and non-selective PLA_2 inhibitors prevent acetic acid-induced colitis in the rat as judged by three indices of inflammation: morphological scoring, assay of tissue MPO activity and measurement of plasma exudation into the isolated colon. PLA_2 may play a role in the pathogenesis of acetic acid-induced colitis and inhibition of the enzyme may offer a mode of treatment in ulcerative colitis.

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Case report

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Delayed perforation of the colon following colonoscopic biopsy

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Colonic perforation is a recognized complication of colonoscopic biopsy, usually manifesting itself within 72 h of the procedure[1]. A case is reported of delayed colonic perforation 9 weeks after biopsy.

Case report

A 50-year-old man presented acutely with a 3-h history of sudden-onset abdominal pain and vomiting. He had a temperature of 37·8°C and clinical signs of generalized peritonitis. Erect chest radiography showed free air under the left hemidiaphragm. Laparotomy revealed purulent peritonitis arising from a punched-out 4-mm perforation in the anterior wall of the distal third of the sigmoid colon. The perforation was not related to a diverticulum and the colon was otherwise normal. The perforation was biopsied and oversewn. The patient made an uneventful recovery and was discharged on the sixth day after operation.

The patient had 9 weeks previously undergone colonoscopy with 'hot' excision biopsy of an adenomatous polyp at 30 cm. Some 2 weeks later he had been reviewed in the outpatient department and had complained of mild aching in the left iliac fossa but was otherwise well with only minimal abdominal tenderness; no action had been taken.

Histological examination of the biopsy revealed extensive necrosis with mixed acute and chronic inflammatory infiltrates. There was granulation tissue formation and evidence of regenerating epithelium, but no signs of neoplasia.

Discussion

Although minimally invasive and generally effective, colonoscopic polypectomy is associated with a number of complications, the two most common being haemorrhage and perforation. Haemorrhage is more common after removal of large polyps (>2 cm) and may complicate up to 2 per cent of all biopsies[1]. Perforation occurs in 0·1–0·5 per cent of biopsies[1,2] and is usually apparent at the time of biopsy or becomes evident within 72 h as the patient develops signs of peritonitis. The present report is believed to be the first of perforation as a late complication of polypectomy. In this patient no other reason for the perforation could be identified, there being no diverticular disease or other colonic pathology. Histological analysis revealed chronic inflammation at the site of perforation, indicating an established injury. The mechanism of perforation is unclear but may relate to a full-thickness burn at the time of biopsy that initially sealed off before breaking down some weeks later.

Clinicians should not rule out colonoscopic biopsy as a cause of symptoms even several weeks after the procedure. This advice may be of particular relevance given the increasingly conservative approach to the management of colonoscopic perforation[2].

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British Association of Endocrine Surgeons Abstracts

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Abstracts from the British Association of Endocrine Surgeons meeting in Bristol, UK, 20–21 May 1993.

Surgical treatment of multiple endocrine neoplasia-related parathyroid disease

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Opinion on the surgical management of parathyroid disease in multiple endocrine neoplasia (MEN) type I is divided between total parathyroidectomy with autotransplantation and subtotal resection. The rarity of MEN II-related primary hyperparathyroidism has not allowed for a well defined policy for this condition. This study compares subtotal (three or more glands) with more conservative resections for primary hyperparathyroidism in MEN I and IIA.

Reported are 135 consecutive surgical procedures performed in 125 patients for MEN-related parathyroid disease, between 1970 and 1991, at a single institution. In all, 106 patients had MEN I and 19 MEN IIA. Associated endocrinopathies in patients with MEN I were islet cell tumours (40 per cent) and pituitary adenoma (42 per cent), and in MEN IIA medullary thyroid cancer (100 per cent) and phaeochromocytoma (32 per cent). Primary cervical explorations for primary hyperparathyroidism were performed in 103 patients (84 MEN I) and 32 secondary or tertiary procedures were performed in 22 patients with MEN I.

When compared with those with MEN I, patients with MEN IIA had a lower median serum Ca^{2+} level at diagnosis (2·65 *versus* 2·82 mmol l^{-1}), were less frequently symptomatic (21 *versus* 51 per cent), had a lower incidence of renal calculi (16 *versus* 37 per cent) and more frequently had apparent single-gland disease (37 *versus* 20 per cent). In MEN IIA, all patients, whether treated by total ($n = 2$), subtotal ($n = 7$) or lesser ($n = 10$) resection, were cured following surgery and none had recurrence over a median follow-up of 5·6 years. Primary and secondary explorations in MEN I resulted in immediate cure of 79 of 84 and 19 of 22 patients respectively. Of primary MEN I operations, failure of immediate cure occurred in three of 16 cases where fewer than four glands were visualized compared with two of 68 where four or more glands were found ($P < 0·05$), and each of these five failed cases had fewer than three glands excised. Among primary MEN I explorations that resulted in a cure, 10-year recurrence rates (Kaplan–Meier) were 21 per cent overall, 22 per cent for those having subtotal resection and 19 per cent for lesser resection.

Parathyroid disease in MEN I and IIA should be viewed as different disease processes and the principles governing surgery for these conditions should differ. In primary MEN I surgery, the aims should be: (1) identification of at least four glands and excision of supernumerary thymic glands to ensure immediate cure; and (2) subtotal resection to facilitate reoperation in the subgroup for whom the disease will inevitably recur. In MEN IIA the aim is to identify and resect all enlarged glands to ensure cure, but routine subtotal resection is unnecessary as recurrence is rare.

Results of surgical treatment for renal hyperparathyroidism

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A retrospective analysis of 67 consecutive patients who had undergone parathyroidectomy for hyperparathyroidism secondary to renal failure was carried out. In all, 35 patients were on haemodialysis and 32 had received a renal transplant. Total parathyroidectomy and autotransplantation was performed in 52 patients and subtotal parathyroidectomy in 15.

Indications for surgery were primarily hypercalcaemia, bone disease and high parathyroid hormone levels in patients on haemodialysis and persistent hypercalcaemia after renal allograft in transplant patients.

Symptomatic improvement after parathyroidectomy occurred in 81 per cent of patients on haemodialysis and 72 per cent of those given transplants. The best predictor of successful relief of skeletal pain after parathyroidectomy was a raised preoperative alkaline phosphatase level. Following total parathyroidectomy and autotransplantation, 25 per cent of patients developed severe postoperative hypocalcaemia, in contrast to none after subtotal parathyroidectomy. There was a good correlation ($r = -0·557$, $P < 0·001$) between hypocalcaemia and preoperative alkaline phosphatase levels.

Of surviving patients, four of 38 after total parathyroidectomy and autotransplantation, and one of 14 after subtotal parathyroidectomy developed recurrent hyperparathyroidism. All five patients with recurrent disease were on haemodialysis (22 per cent).

Transplant patients usually present with less severe disease, have better normalization of biochemical parameters after parathyroidectomy and rarely develop recurrent hyperparathyroidism compared with those on haemodialysis. Patients undergoing subtotal parathyroidectomy have a less eventful postoperative course than those treated by total parathyroidectomy and autotransplantation. However, both procedures result in good control of renal hyperparathyroidism with excellent improvement of symptoms.

Parathyroidectomy in chronic renal failure

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The aims of this study were to evaluate preoperative localization techniques and results of parathyroidectomy in patients with chronic renal failure. A retrospective review of 42 patients was made (23 male, 19 female; mean age 43 (range 21–72) years, mean follow-up 55 (range 1–162) months). Thirty-two patients were on haemodialysis, nine were on chronic ambulatory peritoneal dialysis and one had a transplant. Preoperative localization was achieved in 24 patients using computed tomography (CT) and in 22 using technetium-99–thallium-201 subtraction scanning.

In all, 32 patients had four-gland total parathyroidectomy, of whom 24 had parathyroid reimplantation; one patient underwent subtotal parathyroidectomy. In seven patients only three glands were identified and in two only two glands were found; total excision with reimplantation was performed. Four reoperations were performed for recurrent hyperparathyroidism; three ectopic glands were identified in patients previously shown histologically to have had total parathyroidectomy. Eight of ten patients having undergone three-gland excision had persistent hyperparathyroidism and two of 32 of the alive reimplanted patients have recurrent hyperparathyroidism but remain asymptomatic.

Subtraction scanning correctly identified only 29 of 82 (35 per cent) surgically excised parathyroid glands and CT 55 of 90 (61 per cent). Preoperative localization proved unhelpful except at reoperation when 75 per cent of glands were identified. Total parathyroidectomy with or without reimplantation is the treatment of choice in hyperparathyroidism of chronic renal failure.

Successful allotransplantation of microencapsulated parathyroid glands in rats

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The various roles of parathyroid hormone in metabolism make drug therapy for persistent hypoparathyroidism difficult, but do not justify parathyroid transplantation with immunosuppression. Reduction in immunogenicity of the tissue using culture passages is rarely successful.

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This study examined microencapsulation as a method of immunoprotection while maintaining gland function.

Parathyroidectomy was performed on 280 Lewis and 14 DA rats. After passage in tissue culture for 6 days, 50 per cent of the parathyroid glands of the Lewis rats were microencapsulated, and 10:1 (donor:recipient) isotransplanted ($n = 7$) and allotransplanted ($n = 7$). The other 50 per cent were treated similarly, except for the microencapsulation ($n = 7$ each). Serum calcium levels were tested on the day before parathyroidectomy, and 7 and 14 days afterwards in the donors, and, additionally, every week in the recipients. Successful transplantation was defined as a minimal increase in serum calcium level from $<1{\cdot}6$ to $>1{\cdot}9$ mmol l^{-1}. At 3 months after implantation histological examination was performed on the transplant.

Before the study, all animals were normocalcaemic. After parathyroidectomy, all became hypocalcaemic with a mean serum calcium level of 1·55 mmol l^{-1}. At 6 weeks after transplantation, all isotransplanted and one allotransplanted rat without microencapsulation were normocalcaemic; four isotransplanted and no allotransplanted rats were normocalcaemic after 12 weeks. In the group with microencapsulated transplants, all seven isotransplanted and six allotransplanted rats became normocalcaemic 6 weeks after transplantation and after 4 months four and five respectively were normocalcaemic. Histological examination of functionally successful transplants revealed intact glands or fibrotic remnants of glands. There was no difference in pericapsular lymphocytic and fibroblastic infiltration between isotransplanted and allotransplanted animals.

In an animal experiment, microencapsulated parathyroid tissue, both isografted and allografted, can survive and function in a host. The microcapsule protects the transplant successfully from a foreign-body reaction by the recipient.

Primary hyperaldosteronism cured by unilateral adrenalectomy

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In patients with primary hyperaldosteronism, the surgeon may be reluctant to perform unilateral adrenalectomy if evidence of an adenoma is lacking on imaging studies.

A consecutive series of patients underwent adrenalectomy for proven primary hyperaldosteronism. The efficacy of this procedure as a cure for hypertension and biochemical abnormality was examined.

Between 1970 and 1992, 60 patients underwent surgery for primary hyperaldosteronism. All were hypertensive; five underwent bilateral and 55 unilateral adrenalectomy. The series included 44 macroadenomas ($\geqslant 1$ cm in diameter), nine microadenomas (<1 cm), four associations of macroadenoma and microadenoma, and three cases of unilateral hyperplasia. Tumour pathology was defined in preoperative studies with a sensitivity of 100 per cent for magnetic resonance imaging, 97 per cent for computed tomography, 72 per cent for scintigraphy, 35 per cent for ultrasonography and 100 per cent for venous sampling.

Four of 55 patients remained hypertensive after unilateral adrenalectomy (three of 44 macroadenomas and one of three unilateral hyperplasia) but all had been biochemically cured after surgery. In two the syndrome recurred (two macroadenomas) and one was reoperated on for contralateral multiple 'adenomas'.

Adrenalectomy for unilateral hyperplasia may lead to cure but the syndrome may recur after removal of a solitary macroadenoma. When a firm diagnosis of primary hyperaldosteronism has been made and the unilateral nature of the disease established, the patient should be operated on.

Conn's syndrome: 14 years' experience

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Between October 1978 and October 1992, 55 patients were operated on for primary aldosteronism. The mean age was 50 years. The male:female ratio was equal and there was no propensity of lesions to a particular side. Diagnosis was made in all patients on depressed serum potassium levels, raised serum aldosterone and depressed plasma renin. Localization procedures varied during the period, from ultrasonography to iodocholesterol, computed tomography and latterly magnetic resonance imaging, which was particularly useful in patients who were pregnant. Two women presented in pregnancy, one operated on at full term and one at 18 weeks. A posterior approach was used in all patients, with the exception of one with malignant disease and two with concomitant cholecystitis; these patients were treated transabdominally. The pathology consisted of 51 adenomas, one carcinoma, one doubtful hyperplasia or adenoma and two documented hyperplasia.

There were no operative deaths. In 50 of 51 patients with a single adenoma, potassium level and blood pressure returned to normal. In one patient, the serum potassium level was normal but the patient needed antihypertensive agents long term. In this latter patient the aldosterone and renin levels returned to normal. Of two patients with proven hyperplasia, one was cured by unilateral adrenalectomy and the second had normal levels of serum potassium, but blood pressure remained raised and the patient required antihypertensive therapy. The patient with carcinoma died from metastatic disease 4 years after the original adrenalectomy.

With effective localization, single adenoma can be effectively treated by a simple posterior approach with a high cure rate.

Acute Addison's disease after excision of Conn's adenoma

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Primary hyperaldosteronism caused by a solitary adenoma is usually cured by unilateral adrenalectomy. Postoperative supplementation with steroids is not normally considered necessary.

After a 10-year history of poorly controlled hypertension a 44-year-old man was found to be hypokalaemic. His recumbent morning serum aldosterone level was 1·02 pmol l^{-1} and this rose to 1·65 pmol l^{-1} after ambulation. Morning recumbent plasma renin levels were 1312 pmol l^{-1}, 2007 pmol l^{-1} on rising and 3332 pmol l^{-1} by mid-day after ambulation.

Computed tomography showed a 5-cm mass in the left adrenal gland. A diagnosis of primary Conn's syndrome resulting from an adenoma was made and the patient referred for adrenalectomy. After operation the man remained hypertensive and suffered anorexia and weakness, but was well enough to be discharged 7 days after operation.

Some 2 weeks later the man was readmitted in acute renal failure considered to result from acute Addison's disease complicated by infection. At this time histological analysis of the original adrenal specimen showed a cortical adenoma and cortical atrophy. Adrenal antibodies were found. No cause for the adrenal suppression was found and it recovered spontaneously after 6 months.

This patient may have had a tumour producing glucocorticoid in addition to mineralocorticoid. This possibility should be borne in mind when deciding whether postoperative steroid replacement is necessary after unilateral adrenalectomy in Conn's syndrome.

Vascular invasion in adrenal tumours

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Vascular involvement in 11 adrenocortical adenomas, seven cortical carcinomas (defined by large size, weight or metastasis) and 12 phaeochromocytomas was studied. Four cases of nodular hyperplasia and two of diffuse hyperplasia were examined.

Three carcinomas showed invasion of large capsular muscular veins. One patient died from metastases 2 years after diagnosis. Three of the 12 phaeochromocytomas showed invasion of large veins; no metastases have occurred (minimum follow-up 6 months).

If large vein invasion was present, small capsular sinusoidal vessel invasion was also seen. Necrosis and mitoses, but not nuclear pleomorphism, were associated with large vein invasion. Large vein invasion was not identified in other lesions.

Of the four adrenal carcinomas free of large vessel invasion, three showed small vessel involvement. Similarly, of the nine phaeochromocytomas free of large vein invasion, three showed small vessel involvement. Seven of the 11 adenomas showed subcapsular or intracapsular involvement of small vessels. One hyperplastic adrenal showed involvement of small vessels.

This study confirms that invasion of large veins is an associated, but unreliable, feature of malignancy in adrenal tumours. Involvement of smaller vessels is not significant and may be seen in benign lesions; this feature probably reflects the physiological affinity that endocrine cells have for blood vessels, and may create diagnostic difficulty in some situations.

Influence of changing scanning techniques on gland localization in primary hyperparathyroidism

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The influence of isotopic and ultrasonographic scans on operating time was studied in a series of parathyroidectomies for primary hyperparathyroidism. Localization by scan, operative findings, gland histology and weight were compared. All procedures were carried out by four consultants or with the consultants assisting senior registrars, using a standard operative strategy, aiming to identify all four glands.

Before the use of regular scanning techniques in 1980 the mean operating time was 108·9 min ($n = 22$). This time was significantly improved to a mean of 85·7 min ($n = 102$) with the introduction of ultrasonography and thallium–iodine subtraction scanning ($P < 0{\cdot}0001$). In 1990, new analysis techniques in radioisotope scanning were introduced and only specified radiologists performed the ultrasonographic scans. Despite this, there has been no overall change in the accuracy of ultrasonography (35·6 *versus* 34·1 per cent; $\chi^2 = 1{\cdot}01$, 2 d.f., $P = 0{\cdot}6$) or radioisotopic localization (58·6 *versus* 53·3 per cent; $\chi^2 = 3{\cdot}54$, 2 d.f., $P = 0{\cdot}17$), with no significant improvement in operating time (mean 81·0 min, $n = 44$). During this period the gland weight has decreased significantly from a mean of 330·0 mg to 194·7 mg ($P = 0{\cdot}024$). An incorrectly localized gland causes an increased operating time (mean(s.d.) 85·5(29·8) min), over a failure of localization (79·4(22·9) min), which was only marginally worse than when both scans localized the gland (78·7(23·4) min).

Magnetic resonance imaging in thyroid swelling

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Current imaging techniques such as isotope scanning, ultrasonography and computed tomography (CT) have a variable but restricted role in the assessment of functionally normal thyroid swellings. Although ultrasonography and CT demonstrate the morphology of the gland, their utility is limited by a low sensitivity for neoplasia[1].

As a preliminary to an assessment of the role of magnetic resonance imaging (MRI) in the management of thyroid swelling, the pathological appearances of a consecutive series of 20 resected thyroid swellings were correlated with the images produced from an MRI scanner using a range of imaging software (Siemens Magnetom Impact 1·0 T with A1.3 software and Power Package enhancement) to determine whether any patterns of image exist that may be useful in differentiating thyroid pathology.

No clear pattern or correlation of MRI images with pathology emerged in this early series.

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Influence of inferior thyroid artery ligation on parathyroid function after subtotal thyroidectomy

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In most individuals all four parathyroid glands receive their blood supply from the inferior thyroid arteries (ITAs). The influence of ligation of these arteries on postoperative parathyroid function was investigated in patients undergoing bilateral subtotal thyroidectomy for benign multinodular non-toxic goitre.

In a randomized controlled trial, 100 patients undergoing bilateral subtotal resection for benign multinodular non-toxic goitre were divided into two groups of 50 patients. In group 1 the main ITA was ligated and in group 2 the branches of the ITA were suture ligated at the thyroid capsule. Serum total calcium (Ca), ionized calcium (Ca_{ion}) and parathyroid hormone (PTH) levels were determined before operation and 6, 24 and 72 h after operation. Patients were seen for follow-up after a mean of 7 months.

In both groups 11 patients temporarily required calcium substitution for symptomatic hypocalcaemia in the immediate postoperative period. At follow-up no patient in either group was hypocalcaemic.

	Mean(s.d.) serum level				
	Preop.	6 h	24 h	72 h	Follow-up
Ca (mmol l^{-1})					
Group 1	2·33(0·10)	2·09(0·13)	2·11(0·11)	2·18(0·14)	2·32(0·09)
Group 2	2·34(0·07)	2·09(0·13)	2·11(0·14)	2·17(0·19)	2·34(0·09)
Ca_{ion} (mmol l^{-1})					
Group 1	1·23(0·05)	1·16(0·06)	1·13(0·09)	1·17(0·10)	1·21(0·09)
Group 2	1·25(0·06)	1·15(0·07)	1·13(0·08)	1·17(0·09)	1·21(0·04)
PTH (ng ml^{-1})					
Group 1	46(18)	31(19)	33(14)	35(17)	41(22)
Group 2	41(16)	25(13)	29(14)	32(12)	34(13)

Differences between groups 1 and 2 were not statistically significant. It is of no consequence whether the ITAs are ligated in subtotal thyroidectomy for benign multinodular non-toxic goitre.

Role of parathyroid hormone-related protein in the diagnosis of hypercalcaemia in a screened population

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Parathyroid hormone-related protein (PTHrP) is humorally secreted by malignant tumours. In animal models it has been shown to act on the distal renal tubule to increase reabsorption of calcium via the second messenger cyclic adenosine-3′,5′-monophosphate (cAMP), leading to hypercalcaemia. The diagnostic value of plasma PTHrP levels and its actions on the kidney in humans are unknown but are of great clinical potential.

A screening service for all inpatients with hypercalcaemia was carried out over a 16-month period. Patients had plasma PTHrP and PTH levels measured using two-site immunoradiometric assays. Urine was collected for cAMP and electrolyte measurements. Statistical analysis used the Wilcoxon ranked pairs test and Spearman correlation coefficient (r_S).

In all, 107 patients were screened and a final diagnosis made of 68 with malignancy and 39 with hyperparathyroid disease. Sixty patients with malignancy (88 per cent) had raised plasma PTHrP levels, and in these raised PTHrP correlated with serum calcium ($r_S = 0{\cdot}47$, $P < 0{\cdot}05$), urinary cAMP ($r_S = 0{\cdot}32$, $P < 0{\cdot}05$), and calcium reabsorption ($r_S = 0{\cdot}56$, $P < 0{\cdot}01$). Renal tubular effects seen in patients with raised PTHrP levels were similar to effects in those with parathyroid disease. The use of both assays changed the final diagnosis in ten patients (9 per cent) and therefore improved the differential diagnosis of hypercalcaemia. Although the humoral actions of tumour-derived PTHrP account for hypercalcaemia in the majority of patients with malignancy, hyperparathyroidism should always be excluded.

Reoperation for parathyroid adenoma unsuspected and missed during previous thyroidectomy: lateral *versus* thyrothymic approach

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Of 760 patients operated on for primary hyperparathyroidism, 18 (2·4 per cent) had undergone one or more previous thyroidectomies. Before thyroid surgery seven of the 18 patients presented with hypercalcaemia that had not justified a concomitant parathyroid exploration. Of these seven patients, five had undergone unilateral lobectomy and two bilateral thyroidectomy for benign lesions. In the postoperative course diagnosis of primary hyperparathyroidism was confirmed. Before parathyroidectomy all patients had non-invasive localization studies that were positive in five cases. The mean time between thyroidectomy and parathyroidectomy was 5 years (range 2 months to 12 years).

Because the adenomas were suspected to be outside the area of the initial operation, and to avoid any dissection in the dense scar tissue and fibrosis, two selective surgical approaches were used for reoperation: a unilateral approach for three adenomas located on the side of the remaining normal thyroid lobe and a thyrothymic approach for four lesions located in the thyrothymic tracts. In all patients the approach allowed visualization of a second gland. All patients were cured of primary hyperparathyroidism. There were no recurrent laryngeal nerve injuries and no hypoparathyroidism.

In conclusion, reoperation for unsuspected and missed parathyroid adenoma during previous thyroidectomy can be performed safely if the surgical approach avoids the area of initial operation. Non-invasive localization studies are justified in these patients. The lateral approach is recommended for superior and the thyrothymic approach for inferior glands.

Hypercalcaemia of malignancy: effect of biphosphonate therapy on parathyroid hormone-related protein and renal tubular function

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Parathyroid hormone-related protein (PTHrP) is the major humoral factor causing hypercalcaemia of malignancy (HM). In experimental models PTHrP 1-34 interacts with PTH receptors to increase bone resorption and stimulate calcium reabsorption in the distal renal tubule. Thirty-four patients with symptomatic HM were studied and initial parameters of renal tubular function compared with those of 18 patients with primary hyperparathyroidism. Statistical analysis used Wilcoxon ranked pairs and Spearman correlation coefficient.

In HM, levels of plasma PTHrP 1-86 measured by a two-site immunoradiometric assay ranged from 0·23 to 17·8 pmol l^{-1}, and were undetectable (<0·023 pmol l^{-}) in hyperparathyroidism. Urinary cyclic adenosine-3′,5′-monophosphate (cAMP) and calcium excretion were raised in both groups and did not differ significantly.

In HM following intravenous pamidronate 30–60 mg there was a reduction in plasma PTHrP level (median reduction 0·78 pmol l^{-1}, P = 0·007) on days 3–7 when serum calcium reached its nadir, while serum PTH remained suppressed. In HM at presentation, plasma PTHrP correlated with serum calcium (r_S = 0·49, P < 0·05), urinary cAMP (r_S = 0·32, P < 0·05), and calcium excretion (r_S = 0·54, P < 0·01).

The serum calcium level fell to below 2·6 mmol l^{-1} in 24 patients while calcium excretion in the group as a whole showed a median reduction of 138 μmol per litre glomerular filtrate (P < 0·05). In a subgroup of 16 patients with humoral HM (i.e. no bone metastases), seven failed to respond to pamidronate, while only two of 12 patients with proven bone metastases failed to achieve normocalcaemia (P not significant). In conclusion, plasma PTHrP level correlates with renal tubular function, and a fall in plasma PTHrP level and renal tubular calcium reabsorption has been demonstrated in patients following pamidronate therapy.

Safety of the posterior approach in adrenal surgery

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The advent of laparoscopic adrenalectomy provides the opportunity to assess the advantages and drawbacks of existing surgical approaches. This study reviewed intraoperative and postoperative complications of patients undergoing adrenalectomy via the posterior approach.

Between 1970 and 1992, over 300 adrenalectomies were performed, including 104 via the posterior approach (none of 111 phaeochromocytomas, 38 of 52 Cushing's, 47 of 83 Conn's, four of 20 virilizing or feminizing tumours, 15 of 64 adrenalomas). All tumours were <5 cm in diameter and five were malignant. Adrenalectomy was bilateral in 21 patients (20 Cushing's disease, one Conn's).

The posterior approach was carried out initially in the prone position but currently is performed in the lateral position. A hockey-stick incision was made on the resected 11th or 12th rib.

There was no intraoperative death. During operation, one minimal caval tear and 14 pleural tears occurred and were sutured with pleural drainage in two patients only. One patient died from sepsis after operation. No patient required blood transfusion and none received anticoagulation therapy. All except eight were ambulant the day after surgery. The mean postoperative stay was 4 (range 1–10) days, and after day 4 was justified for non-surgical reasons; it has currently dropped to 2 days.

Adrenalectomy via the posterior approach is safe, comfortable for the patient and allows early postoperative discharge.

Glucose-6-phosphate dehydrogenase activity: a metabolic index in the diagnosis of thyroid carcinoma

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Glucose-6-phosphate dehydrogenase (G6PD) activity in epithelial cells within frozen tissue sections can be measured by quantitative cytochemistry based on the transfer of hydrogen ions (H^+) from substrate G6P to a neotetrazolium H^+ acceptor. This reaction is routinely performed in an atmosphere of nitrogen to prevent H^+ reacting preferentially with oxygen to produce water.

G6PD activity is minimal when benign tissues are reacted in an atmosphere of oxygen but in many malignant tissues a significant amount of G6PD activity is retained in oxygen.

In this study G6PD activity was measured cytochemically in thyroid follicular cells, using frozen sections obtained from 16 consecutive thyroidectomies. Sequential sections cut from thyroid tissue were used for measurement of G6PD activity over varying times in atmospheres of nitrogen and oxygen. Mean(s.d.) maximum G6PD activity was significantly greater (62–89 units) in thyroid carcinomatous than in benign tissues (50·0(3·3) units). A significant decline in G6PD activity compared with that measured in nitrogen was observed when sections from benign tissues were measured in oxygen. In the patients with toxic adenomas and in nine of ten with multinodular goitre, G6PD activity in oxygen declined by 66·2–89·1 per cent (average fall to 76·2 per cent of that observed in nitrogen). In contrast to the findings in benign tissues, G6PD activity in oxygen was unchanged or marginally decreased in the three patients with thyroid carcinoma (one follicular, one papillary, one lymphoma).

The results offer the potential of providing a new metabolic test to complement existing histological or cytological diagnoses of thyroid carcinoma.

Papillary thyroid cancer: retrospective analysis of 760 patients treated in a 20-year period

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The clinical and epidemiological features of 760 patients with papillary thyroid cancer (PTC) (68·9 per cent of all thyroid cancers) treated and followed from 1969 to 1990 were analysed. The outcome was correlated with prognostic factors.

The female:male ratio was 3:1. The mean age at diagnosis was 44 (range 6–85) years with a peak in the fourth and fifth decades; mean follow-up was 5·8 (range 2–21) years.

The presenting symptom was a thyroid nodule in 63·2 per cent of cases; the interval between initial symptoms and diagnosis ranged from 1 to 120 months (<6 months in the majority). PTC was associated with benign thyroid disease, usually non-toxic nodular goitre, in 10·1 per cent of patients and was familial in 2·6 per cent. External radiation in the neck region had occurred in 39 patients (5·1 per cent). Tumour size was <1 cm in 115 patients, 1–2 cm in 137, 2–4 cm in 148, >4 cm in 45 and undetermined in 315.

Surgery was near-total thyroidectomy in 714 patients (93·9 per cent) and subtotal thyroidectomy in 35 (4·6 per cent). According to macroscopic and microscopic pathology, patients were assigned to four groups: class I, intrathyroid disease (401 patients; 52·8 per cent), class II, lymph node metastases (243 patients; 32·0 per cent); class III, extrathyroid extension (107 patients; 14·1 per cent); and class IV, distant metastases (nine patients; 1·2 per cent).

Postoperative treatment included ^{131}I therapy for ablation of thyroid residues and for treatment of functioning metastases, and L-thyroxine suppressive therapy.

Surgical treatment of metastases was limited to a few patients with non-functioning metastases; 40 patients died, 30 from disease and ten as a result of other causes. Tumour-related deaths were significantly correlated with classes III and IV (10·2 and 44 per cent respectively) but not with lymph node metastases.

In this series, significant risk factors were age over 40 years, tumour size >4 cm, extrathyroid extension and/or distant metastases, and subtotal thyroidectomy. Patients with PTC treated with radical surgical and radioiodine treatment enjoy a good prognosis.

Review of current practice in surgical management of benign thyroid disease

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Questionnaires were sent to 95 members of the British Association of Endocrine Surgeons to determine whether there is a uniform approach to the management of patients with solitary thyroid nodule or Graves' disease.

Completed questionnaires were received from 37 surgeons (73 per cent teaching hospital based). Of their clinical workload, 3–100 (median 20) per cent was devoted to endocrine surgery. Fine-needle aspiration of solitary thyroid nodules was performed routinely by 73 per cent of respondents. Of these, 78 per cent described this investigation as significantly altering the number of patients selected for surgical treatment. Total lobectomy and isthmectomy was the operation of choice for 68 per cent of surgeons; 10 per cent did not routinely visualize the recurrent laryngeal nerve. Relapse of thyrotoxicosis after one course of antithyroid drugs was felt to be an indication for surgery by 83 per cent of respondents. There was no consensus as to a lower age limit for radioiodine administration. Of the surgeons, 41 per cent would allow an experienced trainee (registrar in 40 per cent of cases) to perform thyroidectomy in their absence.

There was considerable variation in the surgical management of patients with benign thyroid disease, even among those with a declared special interest in endocrine surgery.

Management of thyrotoxicosis during non-thyroid surgery

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Thyroid crisis is now rarely seen and its treatment is well documented[1]. The management of patients with thyrotoxicosis who require emergency surgery for an intercurrent illness is poorly defined.

Two patients with undiagnosed thyrotoxicosis are presented who required urgent non-thyroid surgery. One patient had a fractured neck of the femur and the other a large bowel obstruction caused by carcinoma of the sigmoid colon. Both patients were rapidly rendered euthyroid with propyl thiouracil[2], iodide and propranolol. Surgery was possible by the start of the second week of admission. Apart from transient sinus tachycardia in one patient, no other complication ensued. The above medical combination is recommended for the rapid control of thyrotoxicosis in patients requiring urgent surgery.

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2. Siersback-Nielsen K, Kirkegaard C, Rogowski P *et al.* Extrathyroidal effects of propylthiouracil and carbimazole on serum T_4, T_3, reverse T_3 and TRH-induced TSH release in man. *Acta Endocrinol (Copenh)* 1978; **87**: 80–7.

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, September, 1210-1211

A selection from the August issue of the American journal.

Use of gene therapy to induce human-mouse xenogeneic chimerism

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Background. *Bone marrow transplantation (BMT) has been used in the laboratory to overcome the immunologic barriers to xenotransplantation and results in chimerism and specific tolerance to donor antigens in lethally irradiated mice. Clinically, BMT carries the considerable risks of graft-versus-host disease and graft failure. Retrovirus-mediated gene transfer could provide a means of introducing foreign major histocompatibility (MHC) genes into host bone marrow cells (BMC) and thus accomplish the immunologic goals of BMT, without the associated risks.*

Methods. *Using a Moloney virus–based vector, a replication defective retrovirus was constructed that contained a complementary DNA encoding the human MHC antigen HLA-A2. Three million C57BL/6 mouse BMC were cocultured for 48 hours with 1 × 10^6 HLA-A2 virus "producer" cells in the presence of 15% WEHI supernatant (interleukin-3) and 200 units/ml interleukin-6. Putatively infected BMC were then used at 2 to 3 × 10^6 BMC/animal to reconstitute lethally irradiated syngeneic mice.*

Results. *Twelve days after reconstitution, spleen colonies were found to have integrated the full-length retroviral sequences. Thirty days after BMT, the introduced DNA could be found in the bone marrow, thymus, and spleen, and approximately 5% of T cells in the spleen expressed the HLA-A2 surface antigen.*

Conclusions. *These data show that xenogeneic MHC genes can be introduced and expressed in mouse hematopoietic cells in vivo and indicate that gene therapy potentially may be used in the future to manipulate the immune system to induce transplantation tolerance. (SURGERY 1993;114:174-82.)*

Composite kidney-islet transplantation prevents recurrent autoimmune beta-cell destruction

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Backgound. *Clinically successful islet transplantation has been rare despite adequate isolation techniques. Reenactment of the original autoimmune β-cell destruction may contribute to the poor results. Distinguishing autoimmune effects from rejection can be accomplished with isogeneic transplants exchanged between diabetes-prone (BB-DP) and diabetes-resistant (BB-DR) rats. These experiments determine the relative sensitivity of islet, whole pancreas, and composite kidney-islet transplants to recurrent autoimmunity.*

Methods. *Acutely diabetic (BB-Ac) BB rats served as recipients of vascularized pancreas, intraportal (IPo) or renal capsular (KC) islet transplants, or vascularized composite kidney-islet grafts from BB-DR or BB-DP donors. Graft function was assessed by daily blood glucose level, and the outcome was confirmed on histologic examination. Cyclosporine 5 mg/kg/day intramuscularly was administered to assess its effect on recurrent β-cell injury.*

Results. *BB-DP pancreases developed recurrent autoimmunity in 55% of cases; cyclosporine afforded complete protection if maintained. Diabetes resistance was transplanted with 23 of 23 BB-DR pancreas grafts; however, islet isolation led to a loss of diabetes resistance for islet grafts to the KC and IPo. Cyclosporine protected KC but not IPo islets. Composite BB-DR kidney-islet transplants functioned indefinitely in all cases.*

Conclusions. *Transplanted islets initally survive by passive diffusion but are ultimately revascularized by capillary ingrowth. The finding that composite kidney-islet transplants function indefinitely suggests that the revascularizing endothelium may play a role in resistance or susceptibility to autoimmune β-cell destruction. (SURGERY 1993;114: 211-17.)*

Extracorporeal life support for adult cardiorespiratory failure

Harry Anderson, III, MD, Cynthia Steimle, MD, Michael Shapiro, MD, Ralph Delius, MD, Robin Chapman, RN, Ronald Hirschl, MD, *and* **Robert Bartlett, MD,** *Ann Arbor, Mich.*

Background. *Extracorporeal membrane oxygenation is routinely used for neonatal respiratory failure but is considered unsuccessful in adults based on old studies and old methods. We conducted a new phase 1 trial of modern extracorporeal life support (ECLS) in moribund adults with cardiorespiratory failure.*

Methods. *Criteria for initiation of ECLS were 90% mortality risk despite maximal conventional care, good potential for recovery, age < 60 years, and no contraindication to anticoagulation. Vascular access for ECLS was performed by operative or percutaneous cannulation. Continuous systemic heparinization was used, maintaining whole blood activated clotting time between 160 to 180 seconds. Blood components were transfused as necessary. Lung management included low rate and low pressure ventilation with an inspired oxygen fraction 0.5 or less.*

Results. *Forty patients were treated with ECLS, 30 with primary respiratory failure and 10 with primary cardiac failure. Twenty-two patients recovered lung or heart function, and 18 patients survived and were discharged from the hospital (14 with respiratory failure and four with cardiac failure, overall survival 45%). The major complication of ECLS was bleeding.*

Conclusions. *With modern techniques, ECLS can be life-saving in adult cardiorespiratory failure when conventional therapy has failed. (SURGERY 1993;114:161-73.)*

Soluble factors modulate changes in collagen gene expression in abdominal aortic aneurysms

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Background. *Although increased procollagen gene expression and synthesis have been implicated in the progression of abdominal aortic aneurysms (AAA), factors modulating this change have not been identified. Furthermore, it is not known whether the increase in AAA procollagen expression is specific to this disease or also occurs in tissue affected by atherosclerotic occlusive disease (AOD). If paracrine rather than autocrine factors are responsible for increased gene expression in AAA, this effect should be transferable to target smooth muscle cells through conditioned media. Our objectives were to determine 1α(I) procollagen messenger RNA levels in AOD tissue compared with normal and AAA and to determine whether differences noted in tissue procollagen gene expression could be transferred through conditioned media from normal, AOD, and AAA tissues to target smooth muscle cells in primary culture.*
Methods. *Normal, AOD, and AAA tissue was used for tissue RNA extraction or was minced and washed with serum-free media (4°C) × 30 minutes and the media applied to human aortic smooth muscle cells (SMC) in primary culture for 36 hours. Total RNA from tissue and SMC exposed to conditioned media was analyzed by Northern and dot blot analysis for 1α(I) procollagen.*
Results. *Relative tissue 1α(I) procollagen levels were not increased in AOD (0.23 ± 0.05) as compared with normal (0.17 ± 0.03); both were decreased compared with AAA (0.53 ± 0.07; $p < 0.01$). The 1α(I) procollagen levels in SMC exposed to conditioned media from AAA (1.73 ± 0.15) were increased ($p < 0.05$) compared with AOD (1.10 ± 0.12) and normal (1.16 ± 0.16).*
Conclusions. *There is no increase in tissue AOD procollagen gene expression. The ability to transfer the same relative patterns of gene expression from tissue to target SMC with conditioned media suggests that paracrine, rather than autocrine, factors modulate procollagen expression in AAA tissues. (SURGERY 1993;114:252-7.)*

Regression of intimal hyperplasia with restoration of endothelium-dependent relaxing factor–mediated relaxation in experimental vein grafts

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Background. *The reversibility of the morphologic and functional alterations that occur in veins transplanted into the arterial circulation was examined in this study.*
Methods. *Common carotid vein bypass grafts (VG) were performed in 20 male New Zealand White rabbits. Ten VG and jugular veins (CV) were harvested after 14 days, and ten VG were reimplanted as venovenous bypass grafts (REV) and harvested after an additional 14 days. Vessels were taken for structural or isometric tension studies to norepinephrine, serotonin, and bradykinin and to acetylcholine and sodium nitroprusside after precontraction.*
Results. *There was a decrease in the thickness of the intima ($p = 0.02$) and the media ($p = 0.002$) in REV compared with VG. In REV, sensitivity to norepinephrine decreased ($p = 0.0007$) with a reduced maximal tension to norepinephrine ($p = 0.02$) and to serotonin ($p = 0.0001$). Bradykinin sensitivity increased in REV ($p = 0.003$ vs VG) and was greater than in CV. Only the precontracted CV and REV relaxed to acetylcholine. All tissues relaxed to sodium nitroprusside.*
Conclusions. *This study suggests that intimal hyperplasia can be reversed with restoration of endothelium-dependent relaxing factor–mediated relaxation but that only a partial regression of the contractile abnormalities can be achieved. (SURGERY 1993;114:258-71.)*

Intercellular communication and maintenance of islet cell mass—Implications for islet transplantation

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Background. *The major emphasis in islet transplantation has been the development of methods to enhance islet purity. This focus assumes that islets do not require support from other cellular elements of the pancreas. We chose to examine a possible duct-islet interaction because of the embryologic origin of islets from ductal epithelium.*
Methods. *Duct and islet cells were prepared by collagenization of hamster pancreas and purified on a bovine serum albumin gradient. Primary duct cultures were passaged twice. Duct-conditioned medium was collected from the tertiary cultures. Three groups of cultures were established: group 1, 100 islets/plate in minimal medium (Dulbecco's modified Eagle medium/F12); group 2, 100 islets + 40 duct fragments/plate in Dulbecco's modified Eagle medium/F12; and group 3, 100 islets/plate + duct-conditioned medium. After a 3-day incubation, tritiated thymidine (1 µCi/ml) was added for 24 hours. The islets were separated from the ducts by handpicking and then sonicated. DNA was measured (µg) fluorometrically and tritiated thymidine incorporation, a measure of cell proliferation, was determined in trichloroacetic acid-precipitated material by liquid scintillation. Data (mean ± SEM) were compared by two-tailed Student's t test.*
Results. *Tritiated thymidine incorporation into islet cells in minimal medium (81.1 ± 24.6 disintegrations per minute [dpm]/µg DNA [$n = 8$ plates]) was less than 25% ($p < 0.001$) of that of islet cells cocultured with ducts (323.2 ± 54.5 dpm/µg DNA [$n = 6$]) or with duct-conditioned medium (389.7 ± 27.6 dpm/µg DNA [$n = 5$]).*
Conclusions. *Pancreatic duct epithelium can stimulate islet cell proliferation in a paracrine manner. (SURGERY 1993;114:423-8.)*

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Laparoscopic repair of perforated peptic ulcer

Sir

The surgical literature is currently flooded by numerous reports describing additional applications for non-invasive laparoscopic technology. Such is the observation of Messrs Walsh, Khoo and Motson (*Br J Surg* 1993; **80**: 127), who offer a novel approach to the laparoscopic treatment of perforated peptic ulcer. The authors perform laparoscopy to confirm or refute the diagnosis of perforation. If confirmed, the presence or absence of a naturally occurring omental patch is noted. If this is absent they convert to an open omentopexy procedure. If there is a naturally occurring omental plug, it is left alone and peritoneal lavage performed through one of the cannulas.

The authors correctly state that they 'see no merit in disturbing an omental patch already in place merely to spend a long time putting it back'. The existence of that naturally occurring omental plug and the notion that it should not be disturbed was described by Taylor and Warren[1] many years ago and applied in the conservative treatment of perforated ulcers. Accurate diagnosis of perforation does not require laparoscopic 'confirmation or refutation'. When spontaneous sealing of the perforation has occurred, as verified by a contrast study[2], most perforations are successfully treated without operation, i.e. without laparotomy, laparoscopic diagnosis or any form of peritoneal toilet[3,4].

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Sutureless laparoscopic treatment of perforated duodenal ulcer

Sir

Laparoscopic treatment of perforated peptic ulcer was first reported in 1989. Various techniques have since been described. Mr Tate and colleagues (*Br J Surg* 1993; **80**: 235) recently reported the technique of omental patching using fibrin glue, but no results were presented. We report the outcome in ten patients with perforated duodenal ulcer who underwent laparoscopic repair using fibrin glue.

Eight men and two women of mean age 46 (range 23–91) years have been treated in the past year. In three cases there was a history of duodenal ulcer. All patients were correctly diagnosed before operation. The median delay between perforation and treatment was 8 (range 2–22) h. Eight patients underwent immediate operation and two had attempted conservative management by nasogastric aspiration for 8 and 24 h.

At laparoscopy the perforation was confirmed as on the anterior surface of the duodenal bulb in all cases. After separation of fibrous adhesions and copious peritoneal lavage (mean 7 litres), the perforation was closed by application of omentum using fibrin glue. A suction drain was placed in the subhepatic region. Postoperative management included nasogastric aspiration for 3 days, with intravenous fluids, antibiotics and antisecretory agents.

The mean duration of the operation was 97 (range 70–130) min. Ileus resolved after a median of 44 (range 18–72) h, with normal feeding resumed by day 6. The mean hospital stay was 8 (range 6–11) days, and there was no associated morbidity or mortality. All patients remain asymptomatic at 3 months. Seven patients have had follow-up endoscopy, which showed incomplete healing in one case only.

Laparoscopic treatment of perforated peptic ulcer is of considerable interest[1,2]. Although peritoneal lavage may be achieved without difficulty, endoscopic suture of the perforation is technically demanding. An alternative technique, with traction of the omentum through the perforation, has been suggested[3] but remains unproven. In contrast, application of omentum with fibrin glue is a simple, quick and safe procedure that has given good results in our experience.

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Emergency laparoscopic surgery

Sir

We were interested to read Mr Paterson-Brown's Review on emergency laparoscopic surgery (*Br J Surg* 1993; **80**: 279–83), particularly in reference to the management of acute appendicitis. This condition has been referred to as 'the great leveller' as diagnostic accuracy has always been poor compared with other conditions, whatever the grade of surgeon. Methods of improving the negative appendicectomy rate include laparoscopy, ultrasonography and computer-aided diagnosis, but these are not widely used.

We recently audited appendicectomy in our own hospital for the year 1991–1992. A total of 126 patients underwent appendicectomy, of whom 34 (27 per cent) had histologically normal appendices. Of these, 19 were male and 15 female. The range of alternative findings was very similar to that in Paterson-Brown's article, and we had 21 patients (13 male, eight female) in whom no pathological reason for symptoms could be identified.

Although Paterson-Brown recommends laparoscopy for *women* before laparotomy for presumed appendicitis, our results suggest that men are just as likely to undergo negative appendicectomy as women and should therefore not be excluded from laparoscopy. It has also been shown that the negative appendicectomy rate is equal in patients in whom the diagnosis of acute appendicitis is 'certain' or 'uncertain'. Perhaps laparoscopy should be performed on all patients before appendicectomy, therefore.

Most appendicectomies are performed by surgical trainees. As laparoscopy becomes more accepted in general surgery, it should become an integral part of basic surgical training. At present it is generally accepted that, if a patient has an incision in the right iliac fossa, they have undergone appendicectomy. As more appendicectomies are being performed laparoscopically, we may require other means of telling whether or not the appendix is still present.

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Laparoscopic resection of a bleeding gastric tumour

Sir

I read with interest the Surgical Workshop by Mr Abercrombie and colleagues (*Br J Surg* 1993; **80**: 373) but would take issue with the ultimate sentence, which implies that there are no risks with laparoscopic resection. This was a surgical procedure requiring 3 h of general anaesthesia with potential morbidity and mortality.

Open resection of small gastric tumours with assessment of the liver and regional nodes is safe in experienced hands. I doubt whether there are data comparing open and laparoscopic approaches to this problem, and until such time as these become available the conclusion drawn is invalid on the basis of a single case.

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Photoplethysmography in the diagnosis of superficial venous valvular incompetence

Letter 1

Sir

The paper by Dr Rutgers and colleagues (*Br J Surg* 1993; **80**: 351–3) concludes that 'photoplethysmography is not the non-invasive method of choice in the routine evaluation of superficial venous valvular incompetence'. This statement may be true for a routine examination used in a group that includes the many varicosities (even large ones) that do not allow sufficient downflow to affect refilling time; it does, however, under-rate the capabilities of photoplethysmography when there is clinical evidence of venous hypertension, such as pigmentation or ulceration. Here, substantial shortening of the refilling time recorded by photoplethysmography is always found. Essentially, photoplethysmography cannot recognize a lesser degree of superficial venous incompetence but can reliably demonstrate when a venous pumping mechanism is proving inadequate, which may be caused by overwhelming superficial incompetence or by defective deep veins. It is here, in the presence of obvious abnormality, that photoplethysmography comes into its own and is able to give positive identification of superficial incompetence as the cause.

In using photoplethysmography for this purpose, preliminary clinical examination should always include a careful mapping out of enlarged superficial veins both visually and by the tapwave technique. Directional Doppler flowmetry is then applied to any suspected pathway of incompetence and in most cases will show the characteristic downflow of simple incompetence after squeezing or exercise; this may be sufficient evidence to decide on treatment. If there is a history suggesting previous deep vein thrombosis or if venotensive skin changes are present, especially ulceration, then photoplethysmography should also be carried out and repeated with fingertip compression to appropriate superficial veins. The use of a venous tourniquet or cuff is a prime source of error, which may cause artefact through venous congestion or be insufficient to prevent gravitational downflow in the superficial veins. Far better is to use localized fingertip pressure over the suspected pathway of superficial incompetence to see whether this causes the recording to revert to normal. Both the presence of such a pathway and its position are thereby confirmed; only clearly repeatable results should be heeded. Superficial incompetence is demonstrated beyond doubt by return of refilling time to normal but, by contrast, deep vein problems will never give this response. If Doppler flowmetry has shown upflow in superficial veins, accentuated by exercise, and the photoplethysmography recording cannot be made to revert to normal by any manipulation to superficial veins, then post-thrombotic syndrome or other deep vein problem is probably present. It is then essential to clarify the cause by functional phlebography or ultrasonographic imaging.

Photoplethysmography should not be discarded too readily. Once its limitations are realized, its use confined to patients with clinical evidence of venous hypertension, and a venous tourniquet or cuff abandoned in favour of localized fingertip pressure, photoplethysmography provides a rapid simple method of distinguishing between surgically treatable superficial incompetence causing venotensive changes and a deep vein state where operation has little place. Air plethysmography is of course a superior alternative, capable of giving quantitative measurement of venous blood expelled by exercise. However, this is more time-consuming and perhaps best reserved for use when results of photoplethysmography are inconclusive.

Photoplethysmography and variants of it remain an excellent initial screening test in the circumstances outlined. The need for brevity in this letter prevents elaboration, but more details have been given elsewhere[1].

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Letter 2

Sir

We read with interest the article by Dr Rutgers and colleagues (*Br J Surg* 1993; **80**: 351–3) comparing photoplethysmography and clinical investigation combined with Doppler ultrasonography in the diagnosis of superficial venous incompetence. They point out that photoplethysmography is not the non-invasive method of choice for routine evaluation. We think that the methods and conclusions need some comment.

First, the number of non-interpretable results of photoplethysmography is strikingly high. Conditions for correct measurement are that the patient should be older than 20 years, the skin temperature higher than 28°C, and it is necessary that the ankle joint has full mobility[1]. Furthermore, it has been recommended that three measurements should be taken to improve the accuracy[2]. In the case of a non-interpretable result one should repeat the measurement.

Second, it has never been claimed that photoplethysmography detects reflux. Thus Rutgers *et al.* compare a method detecting reflux and one that is closely correlated with the venous refilling time. The value of photoplethysmography is shown by the fact that the venous refilling time correlates well with the venous refilling time as measured by the direct invasive phlebodynamometric method (ambulatory venous pressure measurement); this has been shown in several studies[3,4]. This technique is still the ideal standard for the evaluation of venous disease[5]. It allows evaluation of the muscle pump function as well as the resting venous pressure and the refilling time. There is still no comparable non-invasive technique.

Third, it has never been claimed that photoplethysmography alone is optimal for screening of varicose veins. It should always be used in combination with, for example, Doppler ultrasonography. Although the methods overlap, they are clearly complementary[6].

Finally, incompetence of the long saphenous vein can be partial. If only the proximal part is incompetent, this will not influence the refilling time as measured by photoplethysmography near the medial malleolus. The extent of incompetence of the saphenous vein should therefore be described[7].

Light-reflection rheography is a new technique based on the principle of photoplethysmography. Digital photoplethysmography is a further development of light-reflection rheography and is currently the best test available[8]. The instrument adjusts the emitted light until a predetermined signal level of the reflected light is obtained, thus compensating for the different conditions of cutaneous optical density.

In conclusion, photoplethysmography, light-reflection rheography and digital photoplethysmography are inexpensive non-invasive methods to be used in routine phlebological practice. In combination with Doppler ultrasonography they provide a reliable pretreatment screening test for varicose veins.

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Letter 3

Sir

In the paper by Dr Rutgers and co-workers (*Br J Surg* 1993; **80**: 351–3) it is suggested that photoplethysmography is not the non-invasive method of choice for routine evaluation of superficial venous valvular incompetence of the leg. This conclusion is based, in part, on a 22·1 per cent rate of uninterpretable traces and in part on a poor correlation with ultrasonographic findings. Three factors seem likely to account for the conclusion: the definition of an 'uninterpretable trace', the use of a 50 per cent refilling time to solve their problems and the reliance on a single tourniquet. The original definition of an endpoint[1] was the point at which the horizontal baseline was reached for 5 s. Uninterpretable traces were extremely rare in our experience of over 200 studies per month over 12 years, using the Medasonics Photopulse Plethysmograph with the Medasonics PH-77 Phototransducer and using first a low-thigh tourniquet and then a calf tourniquet.

Since the initial report[1] in 1979 and with the progressive sophistication of ultrasonographic equipment, it is our experience that duplex scanning is highly accurate for the quantification and localization of reflux through specific incompetent valve areas. However, unlike photoplethysmography, duplex scanning does not reflect the overall sum of the effects of reflux on the gaiter area – an area of major morbidity. Indeed, single or multiple valvular incompetence can exist without the reflux necessarily being transmitted to the gaiter area. Proper treatment of venous insufficiency includes the treatment of varicose veins themselves and the dermatological changes resulting from this incompetence. Adequate assessment of venous insufficiency requires both the overall quantification of the defect and the determination of the source of venous reflux. Venous reflux photoplethysmography has an advantage over duplex scanning since it permits assessment of the extent to which the abnormal venous reflux is transmitted to the cutaneous tissue in the particularly sensitive gaiter area. Abnormal photoplethysmographic findings related to this area may predict the anticipated morbidity and guide early preventive measures.

While it is true, as emphasized by Van Bemmelen *et al.*[2], that the diagnosis of superficial venous insufficiency by duplex scanning is often 'missed' by photoplethysmography, this ostensibly negative finding is in fact of great prognostic value. A negative photoplethysmography result in the presence of a positive duplex scan probably indicates that, despite evidence of localized insufficiency (superficial or deep), this reflux is not transmitted to the skin of the gaiter area, and the likelihood of severe dermatological changes may be minimal. Thus, venous reflux photoplethysmography remains a valuable, simple, inexpensive and non-invasive tool to assess not only the abnormal venous physiology affecting the gaiter area, but also its source and relative severity. After operation, photoplethysmography permits both short- and long-term follow-up of the degree to which the surgical intervention corrected the reflux transmitted to the gaiter area.

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Anaemia and surgery

Sir

The concern about blood transfusion and surgery[1–3] is exemplified by the Leading Article on autotransfusion and salvaged blood by Messrs Chant and Thompson (*Br J Surg* 1992; **79**: 389–90). Working in a tropical country and being much affected by the shortage and costs of safe blood, we tried to determine more closely the situation in which perioperative blood transfusion is essential. We prospectively examined 3 years (1989–1991) of major operations, both emergency and elective.

The study population was a series of 212 patients who underwent operation but were not transfused during the hospital stay. The preoperative and postoperative haemoglobin levels were recorded plus the amount of blood lost during the operation, the duration of admission (after operation) and the final outcome. The need for blood transfusion was assessed, together with the risk attributable to anaemia during anaesthesia and surgery. Patients were divided into two groups according to the preoperative haemoglobin level, using the traditional threshold of 10 g/dl; there were 106 patients in each group. The test group was defined as patients with a preoperative haemoglobin level < 10 g/dl (mean 7·9 g/dl). Their mean postoperative level was 6·7 g/dl, mean blood loss 650 ml and median admission period 7·7 days. The controls had a preoperative haemoglobin level above 10 g/dl (mean 12·1 g/dl). Their postoperative haemoglobin level was 11·0 g/dl, mean blood loss 495 ml and median admission period 7·3 days. The diagnoses, anaesthetics and surgical operations were similar in the two groups; intraoperative and postoperative management was otherwise identical and the blood volume was maintained with standard methods.

The relation between anaemia (preoperative haemoglobin level and blood loss) and death was as follows. Eight patients died overall (3·8 per cent), but the mortality rate was not related to the preoperative haemoglobin level: three patients died in the test group and five among the controls (P = 0·41). Likewise, postoperative hospital stay was the same (7·7 *versus* 7·3 days, P = 0·79).

The results question current beliefs regarding an acceptable haemoglobin level and the need to transfuse anaemic patients before or after operation; the traditional threshold of 10 g/dl should be re-examined. This study did not examine the precise level below which transfusion decreases mortality rate and above which it is useless or even dangerous (bearing in mind the need to avoid transfusion-associated human immunodeficiency virus and hepatitis transmission). The data do suggest that there is no evidence of increased risk up to a haemoglobin level of 8 g/dl and that the preoperative haemoglobin level alone cannot be a sufficient index for assessing the risk related to anaemia.

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Porcine islet isolation: prospective comparison of automated and manual methods of pancreatic collagenase digestion

Sir

We congratulate Mr Toomey and colleagues for conducting a prospective comparison of automated and manual methods of isolating porcine islets of Langerhans (*Br J Surg* 1993; **80**: 240–3). Although comparative analysis of islet isolation techniques is welcome, manual methods of porcine islet isolation should not be dismissed on the basis of their report.

We have developed a simple inexpensive method of porcine islet isolation[1], in which collagenase solution is injected directly into the pancreas at multiple sites. The gland is cut into small pieces and digested in collagenase solution at 37°C with gentle agitation. No attempt is made to assess accurately the rate of tissue dissociation, and the trauma of tearing apart the digested pancreas is avoided. Intraductal injection of collagenase confers no benefit over direct injection into the pancreas using this isolation process[2].

Table 1 compares islet yields from the pancreas of young Large White–Welsh crossbred pigs using our manual method with those reported by Toomey *et al.*

Table 1 *Comparison of methods of islet purification*

	Leicester		Worcester
	Automated	Manual	Manual
Weight of pigs (kg)	80–100	80–100	15–40
No. of experiments	7	7	6
No. of islets per g pancreas*	4014 (2733–6920)	2698 (2013–5591)	31 380 (14 622–72 400)
Total islet tissue volume (mm^3 per g pancreas)*	3·56 (1·39–5·30)	1·07 (0·46–1·92)	6·03 (2·77–13·30)
105-μm islet equivalents per g pancreas*	5875 (2294–8746)	1766 (759–3168)	9952 (4571–21 975)
Islet equivalent:islet ratio	1:0·7	1:1·5	1:3·2

*Values are median (range)

Islets obtained from these younger pigs were maintained in culture, and they responded to stimulation by insulin secretagogues during perifusion. Although the islet equivalent:islet ratios indicate that smaller and possibly fragmented islets were obtained by our method, the total islet tissue volume exceeded that obtained using the automated process. However, the influence of donor age on the efficacy of islet isolation methods is recognized.

For the purpose of comparison, we have expressed our islet yields on the basis of 105 μm. However, we were surprised that the authors deviated from the internationally agreed islet equivalent diameter (150 μm) used to assess and compare islet yields in large mammals and humans. The presentation of data on this basis may foster confusion and hinder comparison of their results with previously published findings on porcine islet isolation from other centres.

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1. Heald KA, Hail CA, Downing R. Isolation of islets of Langerhans from the weanling pig. *Diabetes Res* 1991; **17**: 7–12.
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Authors' reply

Sir

We are grateful for the interest that Mr Downing and colleagues have shown. Yields of porcine islets depend crucially on the strain and age of pig and, even more importantly, on the batch of collagenase used. Indeed, the batch of collagenase used may influence the yield of islets by up to tenfold. Because these factors vary so much from one laboratory to another, it is not possible to make comparisons between laboratories and we cannot therefore comment on the yields of islets achieved with the strain of pig and batch of collagenase used in Worcester. Our study was designed such that the only variable was whether digestion was automated or manual; the automated method came out on top.

We explained in the paper why we used a 105-μm equivalent islet. If one intends to look at the efficiency of islet isolation by comparing the ratio of islet equivalents to absolute islet counts, then this ratio is relevant only if one uses an islet equivalent diameter derived from the islets within the donor pancreas. We feel that this approach is scientifically correct and should not foster confusion or hinder comparison with results from other centres because, sadly, it is not possible to make meaningful comparison between groups because of the variables discussed.

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Abdominal aortic aneurysm: still missing the message

Sir

The paper by Mr Craig and colleagues (*Br J Surg* 1993; **80**: 450–2) provides an excellent report of the large number of patients who present with ruptured or acutely symptomatic abdominal aortic aneurysm that might have been previously diagnosed and electively repaired. We would like to add a further group of patients, not identified by this study, who should be suspected to have aortic aneurysm until proved otherwise.

We have recently reviewed 87 patients who attended this hospital over the past 11 years with embolic disease affecting either the upper or lower limbs. Follow-up of these patients revealed that two died from ruptured aortic aneurysm during convalescence. One patient died in a convalescent hospital 2 weeks after femoral embolectomy. The other was admitted as an emergency 3 months after embolectomy; a ruptured aortic aneurysm was confirmed at laparotomy. Further deaths from ruptured aortic aneurysm may have occurred at home and not been identified.

Patients who present with embolic disease of the lower limb should undergo ultrasonography of the abdominal aorta to exclude aneurysm as the origin of the embolus.

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Life quality and psychological morbidity with an ileostomy

Sir

We find it difficult to extract any meaningful message from the study by Mr Awad and co-workers (*Br J Surg* 1993; **80**: 252–4). Perhaps attention to the study design factors reported by Fraser[1] in his excellent review would have improved the quality of data generated.

First, the review is retrospective and without a control group. As such the data provide only a 'snapshot' of opinion in a group that has probably become adapted to life with an ileostomy. More meaningful data would have been obtained if the study had been performed prospectively with analysis before and after operation in a patient cohort with ileostomy or by prospective randomized comparison with restorative proctocolectomy.

Second, the response rate is low (82 of 113) and under one-third of the replies are from patients known to have had ulcerative colitis. Such low compliance rates and population heterogeneity lead to volunteer bias with its inevitable effect on validity.

Third, it would be reassuring to know that the subjects were supplied with information on the ileal pouch procedure such that an unbiased informed opinion could be expressed by the participants on the merits and drawbacks of restorative proctocolectomy.

Although quality-of-life measurement is increasingly important in surgical audit, for these measures to influence clinical practice will require a uniform approach with well validated instruments and standard methodology[1].

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1. Fraser SCA. Quality-of-life measurement in surgical practice. *Br J Surg* 1993; **80**: 163–9.

Authors' reply

Sir

Thank you for allowing us the opportunity to comment on the letter from Messrs Kmiot and Bramhall. It is disappointing that they were unable to extract any meaningful message from our study, as we felt that we had made it clear that, in the current climate of opinion regarding restorative proctocolectomy, it is very unlikely that a prospective randomized trial evaluating this procedure against classical panproctocolectomy with ileostomy would now be possible. It follows that an evaluation of the procedure must proceed by other methods, one of which we outlined in our paper. It is surprising that reference is made to the report by Fraser[1] as this paper was published in the same issue of the Journal as our own; short of privileged sight of the manuscript well before publication, we could hardly have taken account of factors mentioned in that study.

Our review was retrospective and without a control group, and the 'snapshot' of opinion referred to was at a mean follow-up of 13 years in a substantial number of patients who naturally had adapted to life with an ileostomy. We contend that the only valid way to assess an operation is at a considerable time after its performance when the trauma associated with the procedure has subsided and when a proper assessment can be made of the quality of life. It is difficult to see, therefore, how more meaningful data would have been obtained if the study had been prospective. Few surgeons in their working life would be able to follow substantial numbers of cases for a long time, and certainly not 44 years, the longest follow-up in our series. Since we do not live in an ideal world, it is therefore unrealistic to expect such studies to be performed prospectively in a randomized fashion for the two operations.

We disagree that the response rate (82 of 113) is low and refer the authors to Bland[2] who states 'the proportion of a sample from whom data is obtained is called the response rate and in a sample survey of the general population is likely to be between 70% and 80%'. The possibility that those lost from our sample may be ill must obviously be taken into account, but we were aware from review of notes available that this was not the case. In a study of mortality among responders and non-responders, Alderson[3], basing his statements of those of Doll and Peto, suggested that the effect of non-response due to ill health at the time of an initial questionnaire had disappeared by the fourth year of follow-up. Our study had a mean follow-up of 13 years. Most of our patients underwent operation for ulcerative colitis; a point brought out in the questionnaire was that few of them seemed to be quite certain of their diagnosis.

The subjects were supplied with information on the ileal pouch procedure, concerning percentage reoperation rate, frequency of bowel motion and complications such as pouchitis. It is impossible to be certain in any questionnaire-based patient survey that bias does not exist, just as it is extremely difficult to obtain unbiased informed opinion from surgeons themselves. The instrument used in our trial to assess psychological morbidity has been well validated and is recognized as the 'gold standard'[4].

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Laparoscopic operations in paediatric surgery

Sir

The Leading Article by Mr Miller (*Br J Surg* 1992; **79**: 986–7) makes interesting reading. The author highlighted the current concept of endoscopic surgery and rightly gave prominence to Semm's pioneering work in laparoscopy[1]. However, laparoscopy in paediatric surgery is not quite as novel as the author suggests. Isakov *et al.*[2] published a detailed account of its use in adhesive obstruction in children, and Blinnikov[3] also used it to assess and treat intra-abdominal adhesions. Comparison of conventional and laparoscopic methods in adhesive obstruction showed advantages for laparoscopy in terms of short hospital stay and early return to school[4,5].

Laparoscopy has been used to exclude surgical intervention in a whole range of non-surgical acute abdominal conditions in children who presented with signs and symptoms of acute abdomen[5]. Dronov (unpublished work) combined endoscopic evaluation of the small intestine with pneumatic reduction of intussusception in infants. The additional use of laparoscopic manipulators could assist the reduction while checking for signs of necrosis and possible perforation.

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1. Semm K. *Endoscopic Intra-abdominal Surgery*. 2nd ed. Wisap, 1984.
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Carcinoid tumours of the appendix in children 1957–1986: incidence, treatment and outcome

Sir

Mrs Parkes and colleagues (*Br J Surg* 1993; **80**: 502–4) report an extensive and interesting study of carcinoid tumours of the appendix in children. However, some of the conclusions based on their data are difficult to accept.

First, consistent histological examination of all appendices in the paediatric age group is recommended. The authors do not state whether residual tumour was identified in the right hemicolectomy specimen of the child with gangrenous appendicitis and a carcinoid tumour. This fact is important since it was the only possible case from more than 40 000 appendicectomies in which histological detection of the tumour may have been advantageous to the patient. Nevertheless, the authors state that their findings 'underline the continuing need for histological examination of all appendices removed from children'. Histopathological examination of appendicectomy specimens in children is important for a variety of well documented reasons[1], but the data presented do not provide a convincing argument based on the detection of carcinoid tumours.

Second, the authors report that appendicectomy alone is confirmed as usually curative, although right hemicolectomy is occasionally necessary. The study provides no support for the latter part of this statement. Appendicectomy alone is adequate treatment for localized tumours $<2{\cdot}0$ cm in largest dimension, but the need for right hemicolectomy for larger appendiceal carcinoids in children is uncertain. In a study spanning six decades at the Mayo Clinic, Moertel *et al.*[2] encountered three patients under 20 years of age with carcinoid tumours of the appendix measuring $\geqslant 2$ cm. In no case was residual or metastatic tumour identified in the subsequent hemicolectomy specimen. None of the tumours reported by Parkes *et al.* was >2 cm in diameter. Histological features such as the depth of tumour invasion are known to be of doubtful prognostic significance in this age group[2].

Third, the importance of long-term follow-up is emphasized. Cases of fatal and metastatic carcinoid tumour of the appendix have been reported in young adults, occasionally after an interval of many years, but either the original tumour in these cases was >2 cm or local metastases were evident at the time of initial operation[2,3]. As in this report, no recurrent disease has been documented in children with appendiceal carcinoid tumours in other large long-term studies[2,3]. Prolonged follow-up is justified in few selected patients.

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1. Chan W, Fu KH. Value of routine histopathological examination of appendices in Hong Kong. *J Clin Pathol* 1987; **40**: 429–33.
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Authors' reply

Sir

We are grateful to Mr Stringer for his interest in our study, the primary aim of which was to describe carcinoid tumours of the appendix from an epidemiological point of view and in particular to assess their incidence and outcome in children.

We respond specifically to Mr Stringer's three points. First, no residual tumour was detected in the hemicolectomy specimen of the child with the gangrenous appendix; the procedure had been carried out on the recommendation of the pathologist, who was of the view that the tumour had extended beyond the mesoappendix. We suggested routine histopathological examination of paediatric appendices since, as Mr Stringer points out, histopathological examination of these organs is already performed for other reasons and the discovery of a tumour would thus involve no extra work. The detection of large, aggressive or partially resected tumours may merit further assessment of the patient and can only be advantageous.

Second, the statement that right hemicolectomy is occasionally necessary was based on the fact that the procedure had been carried out in two of our patients on expert histopathological advice, together with the recommendation of other authors that it should be considered in tumours >2 cm in size. Since we did not find any tumours of this dimension, we could not comment on the need for further surgery in these patients and chose to accept previously stated opinions on such surgical aspects.

Third, we accept Mr Stringer's point that long-term clinical follow-up of the individual patient is indicated only in the circumstances he describes. For epidemiological purposes, long-term follow-up of patients with these tumours, as with all tumours of children, is available through cancer registration links with the National Health Service Central Register. This system has provided us with much valuable information, which has enabled description of the excellent prognosis in these patients.

We appreciate that opinion remains divided on the best surgical management of these patients, and we were not wishing to prescribe procedure or long-term clinical follow-up.

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Laparoscopic herniorrhaphy

Sir

The recent letter by Mr Schraibman on laparoscopic herniorrhaphy (*Br J Surg* 1993; **80**: 538) is interesting but, sadly, very negative. How would surgery ever advance if this were the attitude of all surgeons to new ideas? Of course, for any new procedure to become widely accepted it is necessary that randomized prospective trials be carried out; such a study is already well advanced at St George's Hospital. However, before such trials can be started a reliable technique must be developed to allow worthwhile comparison with conventional alternatives.

Many of the statements in the letter do not stand up to examination. The implication that conventional herniorrhaphy is the 'gold standard' repair with a recurrence rate of only 0·3 per cent and that it is free from complications is simply not consistent with experience in the real world. Indeed, if this were true why have more than 80 different hernia repairs been described? Recurrence rates of up to 20 per cent for primary sutured hernia repair and 30 per cent for recurrent hernia have been reported. Let us not forget that Shouldice had an initial recurrence rate of 17 per cent in 1945 improving to 1 per cent after 5 years[1]. Such figures must surely have been discouraging, but experience luckily continued. Equally 'horrifying' complications occur with open operation and probably more frequently. This seems to have been forgotten in the recent adverse press regarding 'keyhole' surgery. A study of the literature shows a range of complications of conventional hernia repair including ischaemic orchiditis, haematoma, neuralgia, intestinal and urinary fistula, wound infection and, rarely, vascular injury.

We do not accept the comments about a take-up rate of less than 50 per cent by 'informed' patients. On the contrary, despite a full explanation to patients detailing the ongoing experience of the surgeons and the experimental nature of the repair, of over 180 patients offered the procedure since May 1991, only two have refused. Is the method really so experimental? In reality it is merely a new way of doing a well established operation with an excellent record. Evidence from the work of Stoppa, Nyhus, Lichtenstein and others[2] using an open patch technique shows a low recurrence rate; the few that do arise occur mostly in the early postoperative period. This has been the experience of most laparoscopists and, with the refinements in technique and instrumentation that have already taken place, it seems reasonable to predict that recurrence rates will be low. It is interesting that with recurrent hernia even proponents of the Shouldice technique have come to accept that in some cases better results are obtained using a prosthetic mesh[3]. Laparoscopic insertion of such a patch might improve the poor results of open suture techniques for recurrent hernia.

Of course there will be a 'learning curve', but this need not be long and there are already many surgeons experienced in the various techniques, ready and willing to teach in exactly the same apprentice manner as surgery has always been taught. There will be problems, but none should be insoluble. It is the responsibility of surgical teachers to ensure that appropriate tuition is made available to all trainees, and this is essential if we are to maintain the confidence of the public and avoid unnecessary disasters.

We suggest that laparoscopic hernia repair can be performed safely, reliably and cost-effectively, often on a day-case basis. It is likely that hospital costs will remain somewhat higher than for open hernia repair, but not excessively so as the basic equipment is already available. However, costs to the community and society as a whole are much reduced.

Preliminary but mounting evidence suggests that following laparoscopic hernia repair recovery is much quicker, with reduced postoperative pain and the ability to return to normal activities, including heavy work, within a few days of the procedure. However open repair is performed, postoperative discomfort is usually marked and the time off work in this country remains as long as 7 weeks.

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Intermittent claudication incites systemic neutrophil activation and increased vascular permeability

Sir

We feel that there are some inconsistencies in the use of data in the above paper (*Br J Surg* 1993; **80**: 181–4), and have some difficulty understanding the experimental methods as described. Under Materials and Methods, the authors state that stimulation at 10 Hz for 10–15 min seven times a day for 14 days was used as a model for claudication. However, during fluorescence microscopy the muscle was stimulated at the rate of 1 Hz for 10 min, which would seem unlikely to be fast enough to precipitate fatigue as demonstrated in the first part of the experiment.

The authors recorded percentage leucocyte adherence in five post-capillary venules in each rat, there being four rats in each group. This they have considered as 20 different observations. In the statistical analysis, the authors have assumed that the resulting 20 observations are independent of each other and may be treated as from a population of 20 subjects. This is not the case, since these were obtained from only four rats, which for statistical purposes should be treated as four subjects. The authors then state that mean percentage adherence was calculated for each group, and that these data were distributed normally, allowing them to use Student's unpaired *t* test and ANOVA (also for normally distributed data) on four numbers instead of non-parametric tests.

In measuring vascular permeability using the urinary bovine serum albumin:creatinine ratio, the authors state in the text that they used the Wilcoxon rank sum test. We are not certain why some of the data were assumed to be normally distributed, while others required non-parametric analysis from the same experimental animals. Yet in *Figure 5* they have given significance values using Student's unpaired *t* test (for 'normally distributed' data). It is unclear whether these data are distributed normally; *Figure 5* suggests the contrary. We suggest that the Mann–Whitney *U* test should have been used for both leucocyte adherence and vascular permeability, as both Student's unpaired *t* test and the paired Wilcoxon rank sum test appear inappropriate.

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Authors' reply

Sir

Messrs Andaz and Shields appear to have misunderstood our study. The gentle stimulation was not intended to precipitate muscle fatigue but merely to induce leucocyte adherence and changes in vascular permeability, which it clearly did. A 10-Hz regimen would undoubtedly have produced greater changes, but the results would have been impossible to observe owing to the rapid twitching of the muscle.

We believe that the statistical methods used to analyse leucocyte adherence were appropriate; indeed, the addition of ANOVA was suggested by the Journal's referee. Four rats from each group were sufficient to demonstrate an obvious difference between the ligated-stimulated rats and the others; the killing of more animals would have been unjustified.

Differences between groups in bovine serum albumin:creatinine ratios were analysed by the Wilcoxon test as stated in the text. We apologize that the mistaken reference to Student's *t* test in the legend to *Figure 5* was not recognized at proof stage.

We are disappointed that this comment on our paper adds nothing to the understanding of systemic responses to ischaemia and feel that the results displayed in *Figures 2* and *5* indicate obvious differences between groups without the need for didactic statistical debate.

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Statistical comment

Sir

Messrs Andaz and Shields raise two important statistical issues relating to the paper by Mr Hickey and colleagues. The first point relates to the analysis of multiple observations per animal. Unfortunately, neither the original article nor the authors' reply makes it explicit how these data were handled. If, as Messrs Andaz and Shields suspect, the 20 observations per group were analysed as if they were 20 independent observations, then this is a serious statistical flaw[1] that throws considerable doubt on the authors' conclusions. Had the original *Figure 2* shown the actual data points (as was done for *Figure 5*), or had the authors quoted the actual values of the test statistics and the corresponding degrees of freedom (as is recommended in the Journal's statistical guidelines for authors[2]) then this ambiguity would not have arisen, and it would have been straightforward for the reader to assess the appropriateness of the statistical analysis.

The second point relates to the choice of an appropriate statistical test. I suspect that this is more a confusion over nomenclature, which is not helped by a lack of consistency between different statistical texts. The data in *Figure 5* could not possibly have been analysed by a paired procedure such as the (paired) Wilcoxon signed rank test, as the groups are not even of equal size. I can only presume that the authors actually used the unpaired Mann–Whitney *U* test, which is also known as the Wilcoxon–Mann–Whitney test.

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Fully implantable venous access systems

Sir

We read with interest the article by Dr Ramirez and colleagues on fully implantable venous access systems in patients with cancer (*Br J Surg* 1993; **80**: 347–8). We fully agree with the authors' view that these devices are safe, reliable and helpful in treating patients with cancer. In our opinion, the same applies to patients with acquired immune deficiency syndrome (AIDS) requiring intravenous medication and/or parenteral nutrition, although the infection rate of the catheters is considerably higher in these patients because of the underlying disease[1].

Over a 3-year period between December 1989 and December 1992 we implanted 27 Port-a-Cath devices (Pharmacia, Uppsala, Sweden) via the internal jugular vein in 24 male patients with AIDS. Twenty-one patients suffered from cytomegalovirus (CMV) retinitis, one from cryptococcal meningitis and two needed parenteral nutrition. In patients with CMV retinitis the relapse rate of 100 per cent can be reduced significantly by parenteral prophylaxis with ganciclovir or foscarnet[2,3].

Preventing the blindness that usually develops within weeks improves the quality of the remaining life (mean duration 8·5 months). Furthermore, 20 patients were treated in a nursing home or outpatient setting, thus reducing costs of therapy[4]. The infection rate was considerably higher than in patients with cancer (0·31 infections per 100 catheter-days). The mean length of catheter function was 157 days.

Our experience shows that patients with AIDS clearly benefit from fully implantable venous access systems, with improved quality of life and reduced hospital stay.

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1. Johanet H, Saliou C, Marmuse JP, Benhamou G, Charleux H. Implantable devices for permanent venous access. A single-center prospective study comparing an AIDS population with a control population (80 cases). *Ann Chir* 1991; **45**: 497–501.
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Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial

Sir

We read with interest the recent study by Dr Goldminc and colleagues (*Br J Surg* 1993; **80**: 367–70) comparing the results of transhiatal resection with a right thoracotomy approach in oesophagectomy for carcinoma. The operative technique for the right thoracotomy method was not detailed but a reference was given to an earlier paper[1]. This in turn mentions a number of techniques, although the authors latterly appeared to favour the Akiyama[2] procedure, an extensive operation involving laparotomy, right thoracotomy and neck exploration.

We would like to draw attention to an operation that appears to have been largely forgotten, namely the right thoracotomy alone without laparotomy first described by Belsey and Hiebert[3]. Although it does not allow for a wide clearance of the lymphatic drainage, we have found that the duration of survival does not appear to be compromised. Indeed, Dr Goldminc demonstrated almost 100 per cent mortality by 36 months if the nodes were positive whichever of their operative techniques was employed. We believe that the exclusive right thoracotomy approach causes less trauma and is quicker to perform, allowing the unfit elderly population effective surgical palliation and occasional long-term cure.

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1. Launois R, Paul JL, Lygidakis NJ *et al*. Results of the surgical treatment of carcinoma of the esophagus. *Surg Gynecol Obstet* 1983; **156**: 753–60.
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Laparoscopic *versus* open appendicectomy: a prospective evaluation

Sir

I read with interest the recent correspondence from Mr Choy and colleagues (*Br J Surg* 1993; **80**: 399) detailing their early experience with laparoscopic appendicectomy. I am concerned about their stated policy in managing patients who undergo diagnostic laparoscopy for right iliac fossa pain and are found to have a macroscopically normal appendix. They report that the policy is 'as with open exploration, to remove the appendix irrespective of its macroscopic appearance', although the rationale for this is not immediately clear. Presumably, the main reason is the difficulty in correctly diagnosing acute appendicitis, or lack of it, from the macroscopic appearance alone. Indeed, a histopathological study[1] has shown that 19 per cent of appendices described by the clinician as macroscopically normal were found to have histological features of acute appendicitis. In addition, 8 per cent of appendices thought to be acutely inflamed were found to be histologically normal. Discrepancies will exist between surgeons' opinions as to whether an appendix looks normal or is inflamed, and a negative appendicectomy rate by the laparoscopic approach will always occur. However, these figures do not necessarily justify the removal of a macroscopically normal appendix, especially if other lower abdominal or pelvic pathology is encountered. In addition, it is well known that the risk of complications of an operation increases with each additional procedure. The stated policy may also cause diagnostic confusion for a future clinician, bearing in mind that not all patients remember what operative procedure has been performed on them. A small scar in the right iliac fossa is accepted as proof that appendicectomy has previously been performed, but a 1-cm subumbilical laparoscopic scar does not imply the same. The case for preserving a normal appendix has previously been made[2].

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1. Lau WF, Fan ST, Yiu TF *et al*. The clinical significance of routine histopathologic study of the resected appendix and safety of appendiceal inversion. *Surg Gynecol Obstet* 1986; **162**: 256–8.
2. Wheeler RA, Malone PS. Use of the appendix in reconstructive surgery: a case against incidental appendicectomy. *Br J Surg* 1991; **78**: 1283–5.

Authors' reply

Sir

We would like to thank Mr Eriksen for his interest in our report and his useful comments. In a recent report of our early experience[1], we acknowledged that the policy of appendicectomy irrespective of macroscopic appearance is controversial. However, we believe that this is the safest course of action given the discrepancy between macroscopic appearance and histology[2,3]. Diagnostic confusion may arise in future regardless of the policy adopted[4] and may be reduced if appendicectomy is performed in all cases. Although the use of the appendix in reconstructive surgery is well established, relatively few patients require such procedures and we have to balance this against the risk of subsequent appendicitis and its complications. We believe laparoscopic incidental appendicectomy is justified as it can be performed safely and quickly without using expensive disposables.

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Erratum

Macintyre IMC, Wilson RG. Laparoscopic cholecystectomy. *Br J Surg* 1993; **80**: 552–9.

Two of the tables in the above Review contained numerical errors. In *Table* 5, the entry in column three for Soper *et al.*[62] should read 618. In *Table* 6, the entry in column five for Western General Hospital, Edinburgh, should be 4·2 per cent. Apologies to the reader for any confusion caused.

Book reviews

Musculoskeletal Surgery for Cancer – Principles and Techniques

P. H. Sugarbaker and M. M. Malawer (eds). 285 × 220 mm. Pp. 391. Illustrated. 1992. New York: Thieme Medical. DM 198.

For those familiar with the *Atlas of Extremity Surgery* (J. B. Lippincott, 1984) this expanded volume under its new title will be greatly welcomed. No book on musculoskeletal tumours will cover the whole field nor will it include all practices and opinions. This volume deals with tumours of the shoulder and pelvic girdles together with those of the extremities. It does not cover the spine.

A text of 120 pages deals with the clinical presentation, assessment and staging of soft tissue and bone tumours. There are useful sections on phantom limb pain and rehabilitation, together with an overview of chemotherapy and radiotherapy. The remaining 260 pages comprise an atlas of operations, clearly described and with excellent drawings. Each chapter is preceded by a summary. I would commend this well written book to orthopaedic surgeons in training. It is up to date and the references are topical. Naturally, it reflects the practice at one particular centre. For limb-sparing surgery, prosthetic replacement is covered but allografts not.

More importantly, this volume should have a prominent place on the shelves of all orthopaedic departments. It clearly states the dangers of inexpert treatment; any orthopaedic surgeon faced with a tumour is well advised to read this book. There is much at stake for the patient, and for best results tumour surgery should be performed at expert centres.

J. Spivey

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UK

An Aid to Paediatric Surgery. 2nd ed.

R. A. MacMahon (ed.). 240 × 189 mm. Pp. 267. Illustrated. 1991. Australia: Churchill Livingstone. £15·95.

This new edition to *An Aid to Paediatric Surgery* is welcomed as it provides an excellent concise account of the essentials of paediatric surgery for medical students and paramedical staff. It achieves its aims in a volume of 260 pages, is well laid out and easy to read. It is a multiple-author book with the majority of the contributors coming from Monash University in Melbourne, but with the editor being responsible for seven of the chapters there is a pleasant uniformity of style.

There are new chapters on child abuse, sports medicine and ethics. There has been a revision of methods of investigation to include computed tomography and magnetic resonance imaging where appropriate. The illustrations, including the diagrams, are simple and clear, and at the end of each chapter there is a short list of references for further study.

Although this volume is intended for medical students, it would also provide a handy reference for paediatric medical and surgical house staff. The editor is to be congratulated on this new edition, which is thoroughly recommended for medical students during their paediatric training.

J. D. Atwell

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Southampton SO9 4XY
UK

Long-term Results in Vascular Surgery

J. Yao and W. Pearce (eds). 266 × 188 mm. Pp. 494. Illustrated. 1993. Norwalk, Connecticut: Appleton and Lange. US$125.

This 500-page book is a compendium of 40 chapters, all written by different authors, dealing with virtually every aspect of peripheral arterial and venous surgery. The excellent first chapter by Rutherford summarizes the problems in reporting long-term results of vascular operations and suggests some solutions. The book is worth looking at for this chapter alone, which is a model of clarity and sound logical and statistical advice. In general these principles are followed in the many subsequent chapters describing the results of specific procedures, although there are a few where the presentation of data seems biased in favour of the author's preferred position.

Inevitably, there is some overlap between individual chapters and some authors have strayed from the book's original purpose by describing in detail surgical procedures that they favour. Despite these minor shortcomings, the editors have brought together a unique set of reports on the long-term results of vascular operations, making this an ideal reference work. It highlights one of the biggest problems of vascular surgery: the remarkable rarity of large, properly designed, prospective, randomized trials comparing alternative procedures for specific lesions. Despite the large number of descriptive series with long-term follow-up, the uncommitted surgeon will still find it difficult to decide which of several established techniques gives the best results in a particular situation.

The chapters are written mainly by surgeons and there is little mention of adjuvant pharmacotherapy to attempt to improve the results of surgery. There is now quite good evidence that antiplatelet drugs improve the results of most types of vascular surgery, but their use is mentioned only briefly. This book will be an important reference work in all specialized departments of vascular surgery.

J. A. Dormandy

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UK

Vascular Diseases in the Limbs – Mechanisms and Principles of Treatment

D. L. Clement and J. T. Shepherd. 271 × 186 mm. Pp. 319. Illustrated. 1993. St Louis, Missouri: Mosby–Year Book. £57.

Clinicians dealing with vascular disease have forged important links with scientists both in the development of investigations and in experimental work on the pathophysiology of such disease. This book aims to 'provide a bridge between current fundamental and clinical knowledge of blood vessels and their diseases'.

The potential diversity of readership has resulted in a mixture of chapters of widely varying detail and emphasis. There are general chapters on the basic mechanisms of disease that could provide good background reading for a vascular surgical trainee or refresh the memory of his arteriosclerotic mentor. Sadly the 'surgical' content of the book is otherwise rather sketchy and not detailed enough for an aspiring vascular surgeon. There is considerable emphasis on disease of the microcirculation with three chapters on vasospastic disorders and a good critique on methods for assessing the small blood vessels. By contrast, the book covers many investigative methods for large-vessel disease more as a catalogue than with critical or helpful guidance about their place in management.

The interested scientist may find this book helpful to dip into for an overview of surgical practice, and for trainees in vascular medicine it is probably a useful primer. Surgeons are likely to require more detailed texts on investigation and treatment of vascular disease, except for the sections on the microcirculation. Their level of interest in this subject will depend on whether they yet work in cooperation with a vascular physician interested in the microcirculation, who should allow his surgical colleagues to concentrate their expertise on managing disease of the larger blood vessels.

W. B. Campbell

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Notices and announcements

29 September to 1 October and
2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

29 September to 2 October 1993
(dates vary)
Advanced Laparoscopic Surgery Courses
Amsterdam, The Netherlands
Information: Factory/Congress Office, Bloemgracht 169, 1016-KN, Amsterdam, The Netherlands

12–14 October 1993
Noninvasive Vascular Investigation Course
London, UK
Information: Anne Taft, Vascular Unit, St Mary's Hospital Medical School, London W2 1NY, UK

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

27 October 1993
Monitoring and Quality Control During Carotid Endarterectomy
Leicester, UK
Information: Mr A. R. Naylor, Department of Surgery, Leicester Royal Infirmary, Leicester LE1 5WW, UK

1–5 November 1993
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

3 November 1993
Fourth Annual Rush Symposium on Transplantation – Applications of Advancing Technology in Contemporary Hepatology
Chicago, Illinois, USA
Information: Patricia Michaels, Rush Transplant Programs, 1653 West Congress Parkway, Room 201 Jones, Chicago, Illinois 60 612-3833, USA

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Link 8c, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

18–20 November 1993
Combined Meeting of the European Conference on General Thoracic Surgery and 2nd Annual Meeting of the German Society for Thoracic Surgery
Heidelberg, Germany
Information: Administrative Secretariat, c/o AKM Congress Service GmbH, Obere Schanzstraße 18, D-79 576 Weil am Rhein, Germany

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

3 December 1993
Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12 203 Berlin, Germany

21–23 February 1994
Seventh Annual Congress of the North American Society of Phlebology on the Advances in Medical and Surgical Treatment of Venous Disorders
Wilea, Hawaii, USA
Information: North American Society of Phlebology, 523 Encinitas Boulevard, Suite 108, Encinitas, California 92 024, USA

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20 040-030 Rio de Janeiro, Brazil

26–28 May 1994
Surgical Infection Society of Europe 7th Annual Meeting
Vienna, Austria
Information: Professor F. Schulz, c/o Wiener Medizinische Akademie für Ärztliche Fortbildung, Alser Straße 4, A-1090 Vienna, Austria

2–6 July 1994
XVth Biennial Congress of the International Society of University Colon and Rectal Surgeons
Singapore
Information: ISUCRS XVth Congress Secretariat, c/o Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 0316

22–24 September 1994
VIIIth Edmondo Malan International Surgery Days – Difficult Surgical Problems
Parma and Colorno, Italy
Information: Professor G. C. Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43 100 Parma, Italy

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW, Suite 300, Washington, DC 20 005, USA

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to: The Senior Editor, *The British Journal of Surgery*, Blackwell Scientific Publications Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 071-404 1831. Facsimile: 071-404 1927.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

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The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

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The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

COMPLICATIONS OF LAPAROSCOPY AND HYSTEROSCOPY

Edited by R S Corfman, M Diamond and A DeCherney

086542201X, Hardback, £45.00, Jan-93,
288 pages, 86 illustrations

Many surgical procedures in gynaecology are now performed by means of endoscopy or 'keyhole surgery' rather than by traditional surgery, thereby reducing hospital stays and cutting costs. The number and difficulty of such procedures is growing constantly. This book deals with potential complications of such techniques and how to avoid and rectify them.

The contents deal with all the major procedures, including sections on: preoperative and postoperative considerations, anesthesiology, intraperitoneal insufflation and trocar placement, complications arising from vaginal placement of accessories, operative laparoscopy, specific gynecological procedures, hysteroscopy, general surgery and other surgical complications. Their complications are addressed in detail to help the practitioner better understand each procedure and its potential problems.

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- deals with increasingly popular and complicated techniques;
- enables the practitioner to operate more safely;
- responds to the growing trend towards day case surgery.

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Practical Laparoscopy

A G Gordon and P J Taylor

0632036583, Hardback, £29.50, Apr-93,
176 pages, 94 illustrations

General surgery and the surgical specialities are being revolutionised as the application of minimally invasive techniques becomes widespread through all grades. The laparoscope has been and remains at the forefront of minimally invasive procedures both as a diagnostic tool and now more frequently for operative procedures.

This book conveys in a didactic and succinct way the principles of laparoscopic procedure for the younger trainee and the older surgeon approaching the technique for the first time.

- a practical 'how to' book;
- includes descriptions and line drawings of operative techniques;
- emphasis on training and safety;
- information on facilities and equipment required;
- an inexpensive introduction to a technique growing in popularity.

Contents:

Introduction; Instruments; Diagnostic Laparoscopy; Principles of Operative Laparoscopy; Simple Laparoscopy Surgery; Complex Laparoscopy Surgery; Christopher Roysten; Complications; Safety and Training; Facilities for Laparoscopic Surgery; Anaesthesia

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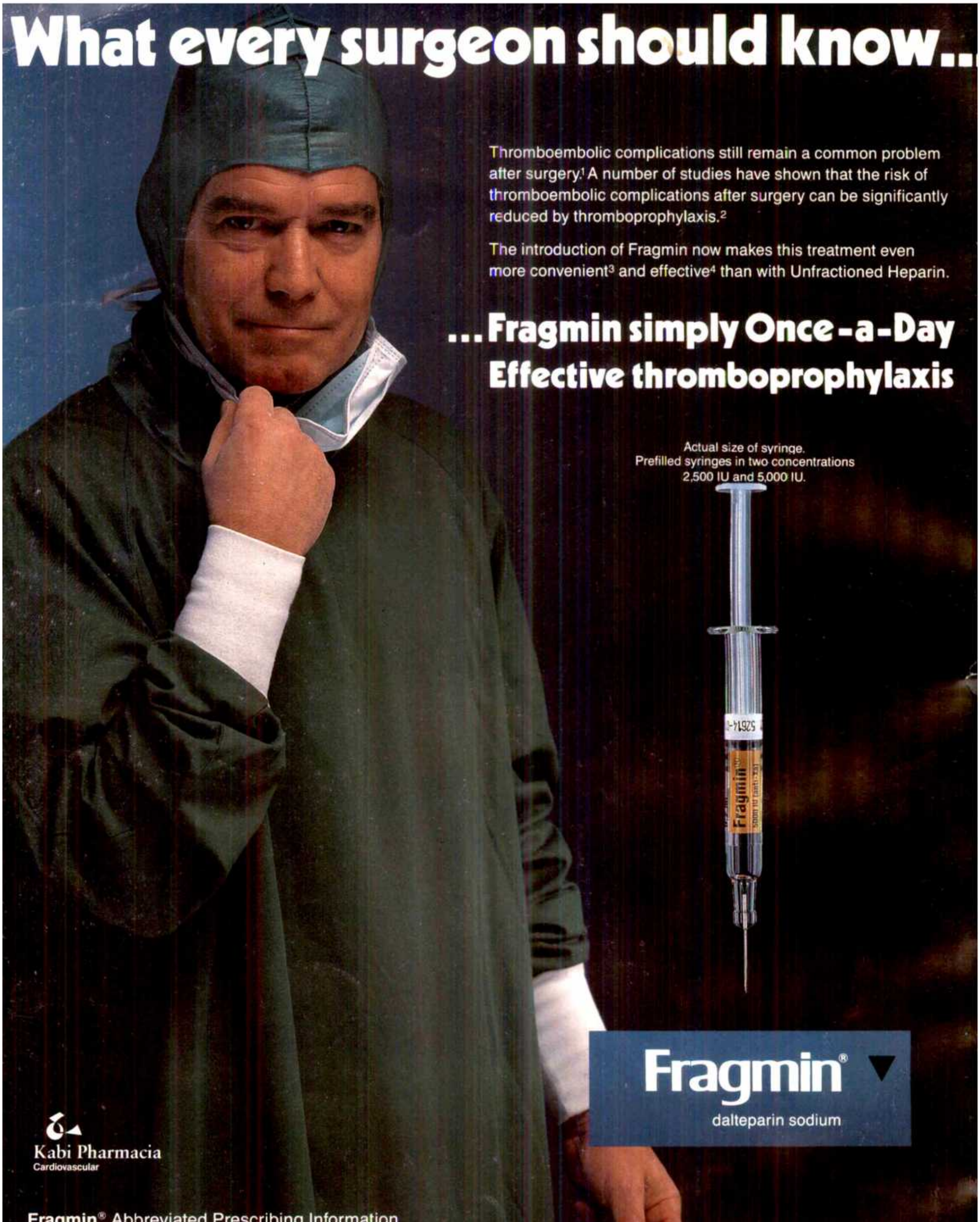
What every surgeon should know...



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Presentation: Single dose disposable syringes containing dalteparin sodium 2,500 IU (anti-Factor Xa)/0.2 ml or 5,000 IU (anti-Factor Xa)/0.2 ml. No preservative present. **Indication:** Peri- and post-operat
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surgery, and the same dose is administered 12 hours later. Thereafter 5,000 IU sc once-daily for five days or until the patient is fully ambulant. **Contraindications:** There are no known absolute contraindicati
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bocytopenia, or defective platelet function and in patients receiving drugs affecting coagulation/platelet function; patients with known heparin hypersensitivity. Fragmin, when administered in doses
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IU/0.2 ml; pack of 10 single dose syringes. 5,000 IU/0.2 ml: pack of 10 single dose syringes. **P L Numbers:** 2,500 IU/0.2 ml 0022/0076. 5,000 IU/0.2 ml 0022/0077. **Kabi Pharmacia Ltd, Davy Avenue, Knowlh**
Milton Keynes, MK5 8PH.

References: 1. Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. 2. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmon
embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. 3. Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weight hepa
given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. 4. Eriksson B I, Kälebo P, Anthmyr B O et al. Prevention of Deep-V
Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

Further information is available from: **Kabi Pharmacia Cardiovascular, S-112 87 Stockholm, Sweden.**

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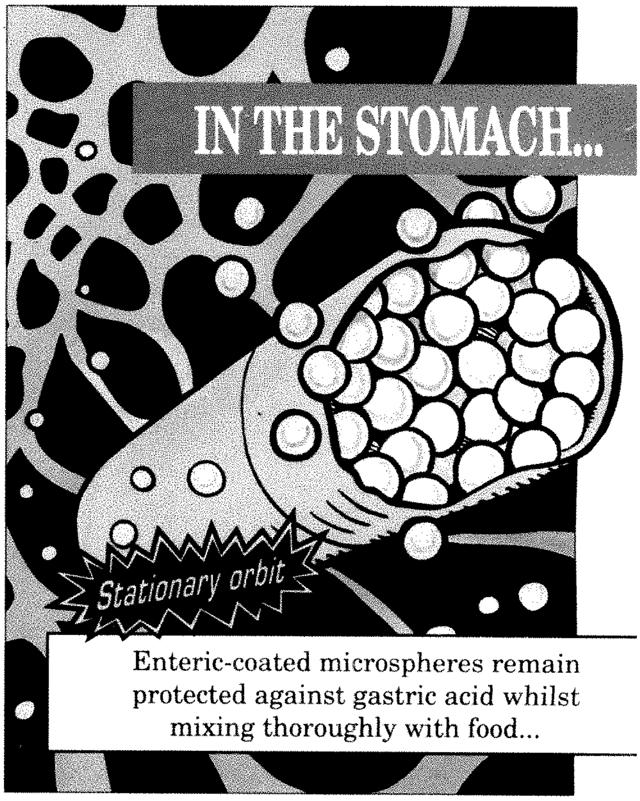

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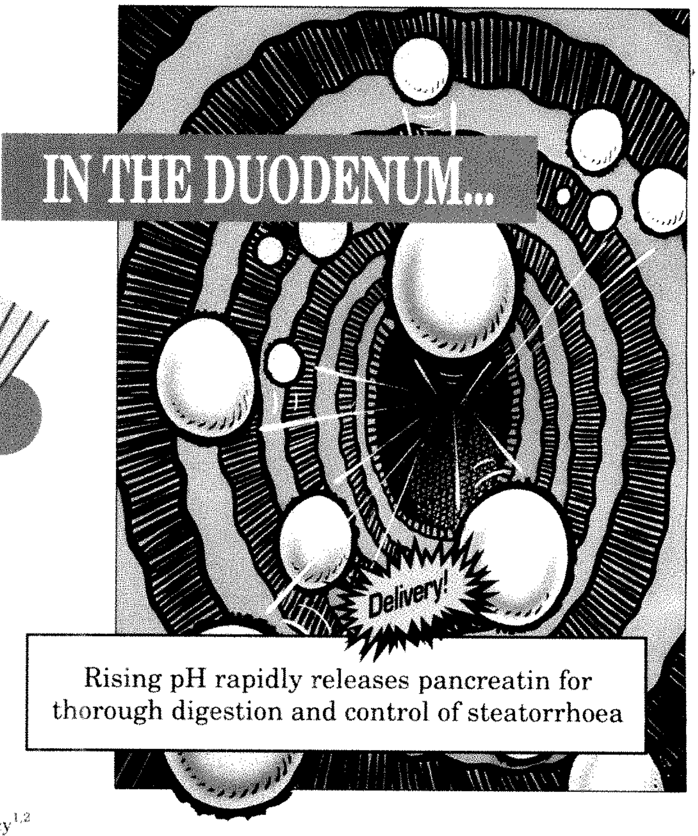
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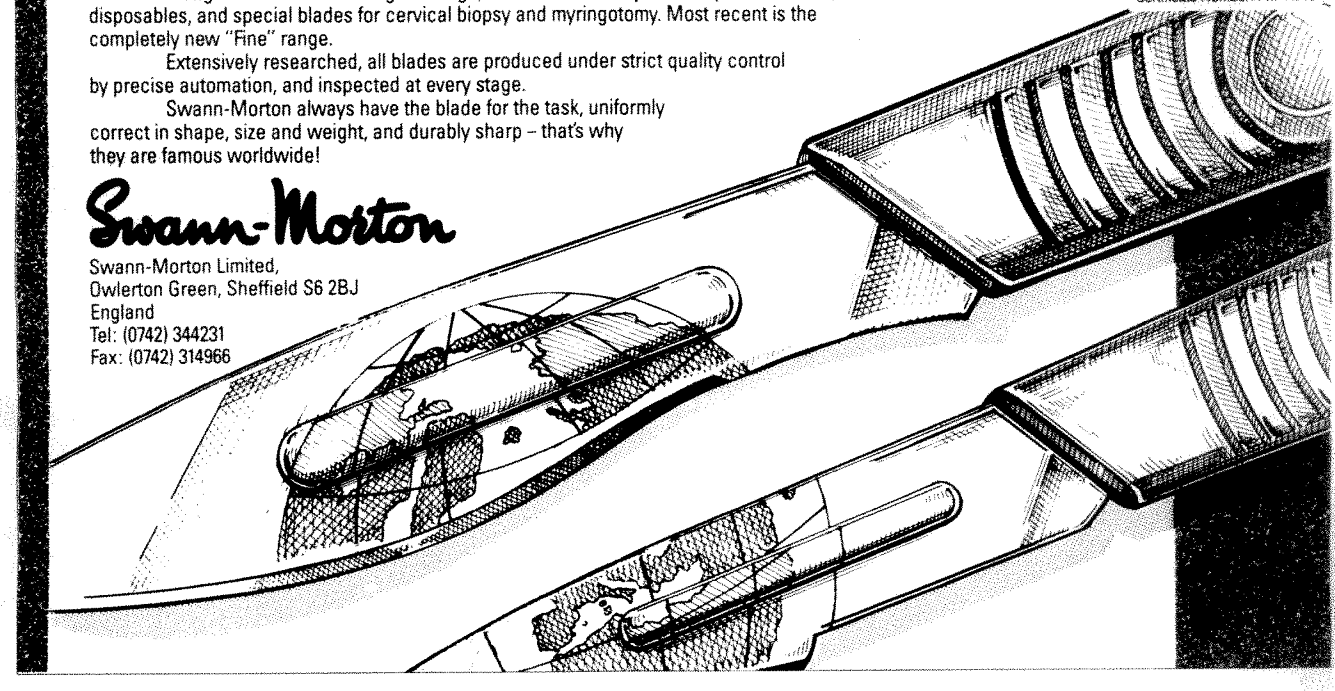

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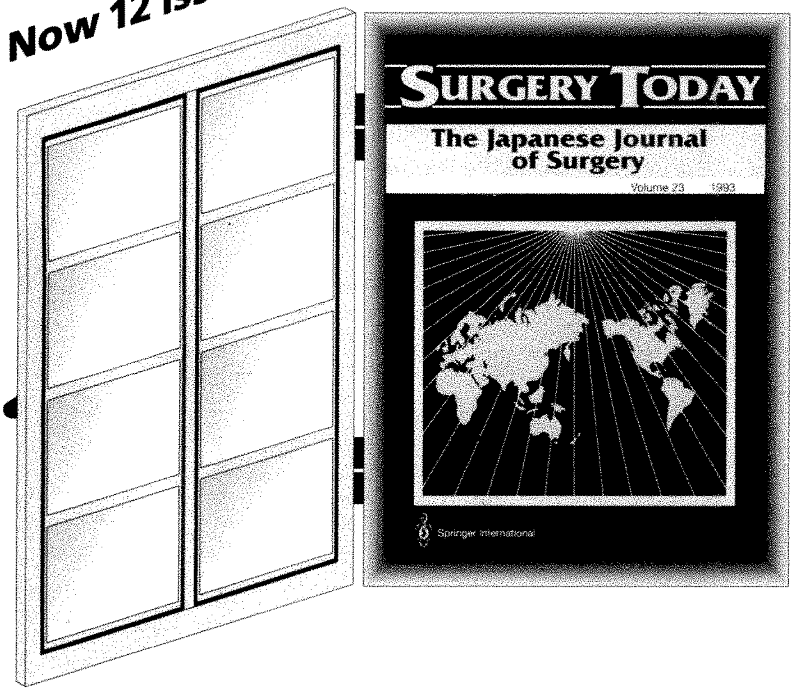

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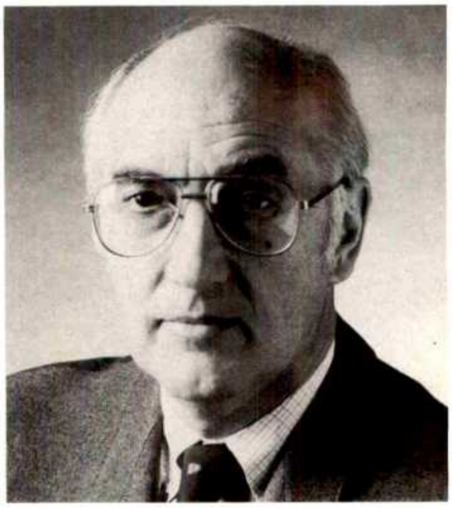

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Br. J. Surg. 1993, Vol. 80, October, 1227–1228

Trauma centres

There is general agreement that trauma care in the UK should be improved and the present arguments are concerned solely with how this may be achieved. In 1988 the Royal College of Surgeons of England Working Party reported on the management of patients with major injuries and recommended setting up 25 trauma centres in the UK, one for each 2 million population and staffed by 24-h consultant cover[1]. A first step forward was the introduction of the American Advanced Trauma Life Support courses by the College for improving the training of doctors in trauma care[2]. In 1992 the Department of Health identified accident treatment as one of the six priorities for healthcare in the future. Financial support was given by the Department for four centres – Stoke-on-Trent, Hull, Preston and the Royal London Hospital – with subsequent evaluation of different aspects of their trauma systems. These have become *de facto* trauma centres, but that does not exclude other hospitals performing the same function. The subject of this article is trauma centres as recommended by the Royal College, but it must be emphasized that complete trauma care consists of prevention, treatment and rehabilitation; a total system is required. Treatment consists of prehospital care (depending on trained personnel as well as transport and communication) and care in hospital (depending on emergency room staff, theatres, intensive care units and all the professional personnel in the hospital). Trauma care does not belong to any one person or department.

Before the Working Party report, a study of 1000 deaths from trauma showed large and unacceptable variation in results between centres[3]. The 1000 patients were divided into half who died before reaching hospital and half who died from possibly avoidable causes in hospital. Prehospital deaths that were avoidable by better care at the scene were not studied, but the large number that occurred at the accident scene emphasized the importance of the ambulance service, its trained personnel, its communication system and its transport. Improvement in trauma care must include a closer integration of prehospital and hospital services.

The original plan for the 192 districts in England and Wales was to have one district general hospital and one acute emergency department per district. The aim that each accident and emergency department should have one or more consultants has never been realized. This system was supposed to provide uniformly good emergency care, but it is now criticized. Furthermore, there are suggestions that many of the accident and emergency departments in London should be closed and that the functions of two or three in a group could be centralized.

What is being done at this moment to improve trauma services? The Department of Health has accepted the criticism that improvement should occur but has neither agreed nor planned 25 trauma centres. Instead, it has commenced an evaluation of the four trauma centres at Stoke-on-Trent, Hull, Preston and the Royal London Hospital. Professor Brian Williams, director of the Medical Care Research Unit at Sheffield, was chosen to research these four systems so that the government could make logical decisions. The two main projects are, first, an evaluation of regional trauma care systems comparing Stoke with the 'normal' district general hospitals at Hull and Preston, and, second, an evaluation of the Royal London Hospital's enhanced Helicopter Emergency Medical Service[4]. The research group is interested in prehospital care, so there is a further arm of the London study which will assess the effect of land ambulances staffed by personnel with enhanced training (paramedics). The same team is undertaking another study of the West Country helicopter service in Cornwall and the Sussex Police Helicopter Emergency Service. Both of these differ from the Royal London Hospital helicopter service in that they do not have suitably trained doctors on board.

Endpoints of the evaluation are in terms of mortality and morbidity. Major Trauma Outcome Study-type information will be collected. Morbidity will be recorded using global instruments of disability and correlated with the original trauma severity, measured by the North American Anatomical Injury Severity Score, and the physiological response, using the Revised Trauma Score.

Costs will be assessed for all the hospital and transport systems. 'Marginal' costs of cases brought in by helicopter will be calculated adding the costs of this transport

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system to those that would normally occur if the patient came to hospital by land ambulance. Cost–benefit will be calculated by matching costs and marginal costs with the benefit of improved care, taking into account death and the expense of disability to the individual, his or her family and society. The mathematics are daunting because the cost of the premature death of a young person from a road traffic accident is now calculated by the Department of Transport at about £700 000; this includes such items as widow's pension, child allowance, loss of earnings, loss of production and loss of tax paid to central government (the Department of Health does not accept this figure). A further assessment will be made of which particular factors are most important in each of the different trauma care systems under evaluation.

Evaluation of the Greater London system, which is the only fully integrated helicopter emergency medical system with a doctor and paramedics on board, will be completed early in 1994. The study of the Sussex and Cornwall air ambulances, which are not directed specifically at trauma, will be completed later. The Stoke, Hull and Preston evaluation was started only in 1992 and will not be ready until 1994–1995. It should be understood that these three centres are not typical district general hospitals because all three have in-house neurosurgery units. Another difference is that Stoke has a team of six consultants who provide continuous 24-h cover for the 168-h week. If results vary between different systems, details must be examined to include prehospital transport, on-scene treatment and call-out systems.

The following statements are offered as a basis for discussion before decisions are made about building the suggested 25 trauma centres. The Department of Health evaluations will be ready in 1994–1995 and should provide the data needed for informed decision making.

1. Trauma care should include prevention, treatment and rehabilitation.
2. Treatment includes prehospital care, with rapid transport by land ambulance or helicopter and highly trained ambulance personnel with or without doctors, and care in a hospital that has all the local acute district general hospital services and immediate access to essential regional specialties by fast secondary transport.
3. Prehospital treatment saves lives by avoiding death from respiratory or circulatory causes. This must be improved and the paramedics integrated into the hospital services.
4. Hospital care may result in death from an avoidable cause. Early surgery and adequate intensive therapy are essential. Consultant-led teams experienced in multiple trauma should be encouraged.
5. Since the majority of hospital deaths result from head injuries, a neurosurgical unit should be associated with every trauma centre. The corollary is that no neurosurgery unit should exist in isolation from an acute general hospital.
6. All neurosurgical and other specialist units (burns, maxillofacial, cardiothoracic, transplantation) should have helipads to facilitate secondary transport. Ideally they should be integrated into acute hospitals.
7. Closure of some hospitals, and accident and emergency departments may eventually lead to others taking on the form of a trauma centre, with the essential specialty mix. This does not imply a UK network of expensive new trauma centre hospitals.
8. The ideal system of trauma care has not yet been agreed but any improved system should exist on a national scale, be available to the whole population and be paid for by the National Health Service.

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Laparoscopic surgery for colorectal cancer

There are two authors of this article because it is necessarily a debate, the gift of reliable prophecy being in general denied even to surgeons. The laparoscopic revolution is rocking the foundations of our institutions and changing every branch of general surgery. It is now urgent that its scope and limits should be defined.

A recent BBC *Newsnight* programme, not sharing our diffidence about prophecy, told the public that 80 per cent of abdominal operations will soon be performed through the laparoscope. The younger author (N.A.O'R.) is impatient to conquer the remaining 20 per cent; the older (R.J.H.) has difficulty believing that the most demanding procedures will ever be better performed without conventional open exposure. The virtual loss of tactile input, the reduced ability to apply direct pressure to control bleeding or to retract powerfully to display tissue planes, the current limitations of two-dimensional video, and the tedious completion of a knot that would formerly have taken seconds, all appear to the senior author to be insurmountable obstacles. Is he in danger of becoming a 'beached whale', his world inherited by the 'young lion' with the laparoscope?

Despite the misgivings of many, demanding colorectal laparoscopic surgery is being performed, in Britain and around the world, for both benign and malignant disease[1–3]. The required skills and training are considerable and the 'learning curve' daunting. All agree that simpler procedures must precede surgery for cancer; rectopexy and colonic resection for benign disease allow surgeons to refine techniques of dissection and to observe for themselves the essential steps of precise rectal mobilization. But is laparoscopic colorectal cancer surgery really worth all the time and expense? Can the young lion persuade the beached whale?

Abdominoperineal operations can now be performed without a significant abdominal incision, anterior resection with only a 5-cm wound. Patients have less pain, mobilize sooner and appear to suffer less paralytic ileus and fewer infective problems; but are we sacrificing long-term survival for the sake of a little less pain? We do not yet know local recurrence rates after these new procedures but it seems sensible to assume that long-term outcomes will depend on adherence to established oncological principles. We both believe that resection of a precisely defined tumour package around the primary lesion is the chief determinant of surgical cure[4]. Careful dissection is needed, as is reasonably proximal pedicle ligation and the prevention of abdominal or staple-line contamination by luminal contents. An unprotected specimen must not be squashed against parietal tissues on removal.

Dissection with the laparoscope should be identical to that achieved at open operation. We agree with Monson *et al.* that the view low in the pelvis may even be better using the laparoscope, but this is not always so as it is easy to stray into the mesenteric fat and create irksome bleeding that can render accurate dissection impossible[1]. Access to the 'holy plane' of rectal surgery can readily be achieved posteriorly and anteriorly, but staying in the plane laterally can be difficult[5]. Herein lies the basic message: if an accurate tumour excision cannot be done, conversion to an open procedure must be the rule. The surgeon's good judgement should be applauded rather than surgical timidity condemned.

Instrumentation for minimally invasive surgery is becoming both better and more expensive all the time. Use of reusable tools must be encouraged. An extra expenditure of between £500 and £1000 is required to fashion an intracorporeal laparoscopic anastomosis after dividing both bowel and vascular pedicle with cutting staplers. The proximal extent of vascular and lymphatic clearance should be the same as that achieved by open surgery. Spillage of luminal contents must be avoided; cutting staple guns can reasonably isolate bowel contents but they may also increase suture-line recurrence by crushing downstream tumour cells into the staple line. A triple-staple technique might facilitate intraluminal washouts below the first staple line and so guard against implantation, as we believe to be necessary[6].

The present generation of laparoscopic staple guns does not always allow low rectal division, especially in the narrow pelvis. We are concerned by the high percentage of abdominoperineal operations in a recent unselected series[2]. One would hope that this reflects an unusual referral pattern and not a tendency to take the easy way out and create a 'minimally invasive sphincter sacrifice'. It may be that ultralow and even low anterior resection for middle- and lower-third rectal carcinoma should remain in the domain of conventional surgery. Considering his

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special interest operation – total mesorectal excision – the senior author can see no alternative to finger and thumb compression of the rectum just distal to the palpable lower edge of the tumour. This is essential before accurate placement of a clamp across the muscle tube beyond the mesorectal 'capsule' of tissue prior to cytocidal washout. This technique has made possible 50 'close shave' sphincter-saving procedures in Basingstoke for lesions 4–6 cm from the anal verge[7].

The prolonged duration of laparoscopic procedures is a major concern. Not only do they take up valuable and often scarce list space but 6–8-h operations must increase the risk of thromboembolic complications. Experience does shorten operating times but even highly skilled surgeons may find progress painfully slow. Once again, judgement is required and conversion to open operation in such circumstances is often prudent. Once resected, the specimen should have a clean mesenteric edge and leave an empty tumour bed. Lymph node counts are reported and laudable but may not tell the whole story[1,2]. A ragged or shredded specimen may contain more lymph nodes but must imply a greater risk of residual tumour or intraperitoneal seeding. It may be that a photographic record coupled with better margin examination such as that suggested by the pathologists Quirke and colleagues[8] will give a more reliable indication of the adequacy of cancer clearance.

As first noted by Fielding *et al.*[9], variability among surgeons is obvious in terms of local recurrence of rectal cancer, rates of 5–40 per cent being reported. One may expect that laparoscopic procedures will have a similar spread but it will be a tragedy if poor outcome is perpetuated for the sake of smaller incisions. Unfortunately, such surgical variation devalues the potential worth of a multicentre trial, but laparoscopists must strive to achieve the excellent results now being produced by experienced rectal operators, and the new methods must be audited by every practicable method. A prospective register of all patients *without exclusion* is overdue; the public is ill served by the under-reporting of mishaps for fear of ridicule or litigation.

No surgeon should embark on a laparoscopic operation for cancer until he or she has watched and been convinced by pictures of satisfactory dissection and 'emptied' tumour beds on the video screen by those who advocate the method. With the arrival of sophisticated electronic imagery, it has never been easier for one surgeon to show another exactly what has been achieved. Despite considerable personal experience and having observed many international experts, neither of us has yet seen or reproduced proper total mesorectal excision laparoscopically. The senior author remains unhappy even at the cancer clearance achieved at more proximal colectomies. A recent warning by Wexner[10] that four separate port recurrences have been publically reported after resection of Dukes' A or B carcinoma suggests that tragedies may be occurring in the wake of the new technology.

Certain laparoscopic techniques can benefit patients with cancer. Palliative resection, abdominoperineal excision 'top end', splenic flexure mobilization, reversal of Hartmann's procedure and stoma creation are obvious examples. When operating for cure, however, we cannot condone compromise of the established principles that have made colorectal cancer the one commonly curable visceral malignancy.

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Complications of circumcision

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Circumcision remains a common operation, with over 30 000 procedures performed annually in the UK, mostly on children. The British Medical Association has recommended that circumcision should be performed only for medical reasons. Despite this, controversy exists over whether too many circumcisions are being performed. Are patients being exposed to an unnecessary operation? It may be argued that in doubtful cases it is easier to proceed to circumcision on the assumption that the attendant risks are low, but the operation is associated with a definite morbidity and rare deaths have been reported. This review considers the spectrum of complications that may result from circumcision and discusses the possible aetiological mechanisms.

Circumcision is probably one of the oldest of all surgical procedures. Although the origin of the practice is not entirely clear, it almost certainly began as a religious rite. That it was practised by the Egyptians is evident as the earliest mummies were found to be circumcised. In the Jewish community circumcision remains a religious ritual and is usually performed on the child's eighth day of life by a *Mohel.* Religious circumcision is also practised by Muslims; the procedure is performed between the ages of 4 and 13 years. Curiously, however, the Koran contains no specific ordinance on this subject. Currently, approximately one-sixth of the world's male population is circumcised, mostly on religious grounds. In Western society circumcision is usually performed for medical reasons, the commonest of which is phimosis[1-3]. There is, however, enormous variation between the circumcision rate in the UK (5-6 per cent[1,4]) and that in the USA (80-90 per cent[5-7]). This large discrepancy exists despite recommendations from both the British Medical Association[8,9] and the American Association of Pediatricians[10] that circumcision should be performed only for medical reasons.

The aim of circumcision is to excise sufficient foreskin (both penile shaft and inner preputial epithelium) to leave the glans uncovered. As an alternative to circumcision some advocate the technique of 'preputial plasty', where a longitudinal incision of the phimosis constricting band is followed by transverse suture[11]. Apparently more popular in Europe, it is a method that has yet to find favour among surgeons in the UK. There are many different techniques of circumcision but they can be broadly classified into four types: dorsal slit, shield, clamp and excision[12]. All these techniques have their strengths and limitations together with their protagonists and critics. More often than not, however, complications arise as a result of operator inexperience rather than of the method employed. All techniques aim to provide the best cosmetic result together with the lowest possible morbidity rate; in this respect the key factors to be observed are attention to asepsis, adequate but not excessive excision of the inner and outer preputial layers, haemostasis and cosmesis[12]. Some authors have reported a complication rate as low as 0·06 per cent[13], while at the other extreme rates of up to 55 per cent[14] have been quoted. This reflects the differing and varying diagnostic criteria employed; a realistic figure is 2-10 per cent[3,12,15]. Although haemorrhage and sepsis are the main causes of morbidity, the variety of complications is enormous. The literature abounds with reports of morbidity and even death as a result of circumcision.

Operative complications

Haemorrhage and sepsis are the commonest complications and are considered in greater detail below. The nature of circumcision dictates that errors of omission and commission, i.e. too little or too much, in assessing how much foreskin to remove are likely to happen, and one of the commonest complaints is of an unsatisfactory cosmetic result. If insufficient foreskin is removed the cosmetic appearance is such that the penis does not appear to have been circumcised; phimosis may still subsequently develop. In a series of consecutive circumcisions in Australia, Leitch[16] found that in 9·5 per cent of patients the operation had to be repeated because of inadequate skin excision at the initial procedure. MacCarthy *et al.*[17] reported this figure to be 1 per cent in a study from the UK. In a more recent series from Israel, where religious circumcision is widespread, of 60 children referred following potentially inadequate circumcision 42 required recircumcision; the majority of these children were operated on before 4 years of age[18]. The rest were treated conservatively and had a satisfactory cosmetic result at follow-up to 10 years of age. Insufficient excision of the foreskin and inner preputial epithelium may result in wound contraction and cicatrization of the distal foreskin. The fibrotic ring so produced may result in true phimosis, an event observed in 2 per cent of cases in one UK series[15]. In severe cases urinary obstruction may ensue[19].

Removal of too much skin from the penile shaft may be caused by pulling it over the glans during operation. After foreskin excision the remaining skin slides back, leaving a denuded shaft. Others suggest that such penile denudation injuries occur as a result of failure to break down the ventral foreskin adhesions to the glans penis completely[12,20]. It is therefore essential that, before any incision is made, the inner preputial epithelium is completely free from the glans such that the entire coronal sulcus can be visualized. Penile denudation injuries may occur as a result of sepsis[21], from diathermy injury[22] or from injected substances mistaken for anaesthetic solutions[22]. The majority of cases can usually be managed conservatively with a satisfactory cosmetic and functional outcome[21,23-25]. Such injuries in adults may be managed conservatively if the defect is less than half of the total penile skin. Complete denudation in the adult is managed by split-thickness skin grafting for optimum cosmetic and functional results[21,23,26]. Of three cases encountered by Gee and Ansell[24], one child with complete denudation had initial treatment by burial of the penis in a tunnel of scrotal skin; no follow-up was available on this patient. Use of a pedicled scrotal skin flap has recently been described for the reconstruction of penile shaft skin[27].

A rare consequence of excision of excess preputial skin is the so-called 'concealed penis'[23,25,28,29]. Kaplan[12] maintains that, although an excess of skin is removed, not enough inner preputial epithelium is excised. The new preputial orifice is,

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therefore, distal to the glans, and as healing and fibrosis occur the penile shaft is forced into the suprapubic fat, with the resulting preputial ring at the level of the skin of the mons pubis. Other suggestions about the aetiology of this complication include a tendency of the penis to retract into the fatty mons pubis[29] and the possibility that the penile shaft is forced into a subcutaneous position by wound contraction[25]. Subsequent fibrosis of the circumcision wound leads to stenosis of the preputial orifice, which then traps the penile shaft subcutaneously[23,29]. Treatment of this condition is surgical correction. In the presence of phimosis, Kaplan[12] recommends a circumferential incision at the preputial ring to avoid the need for skin grafts to achieve coverage of the penile shaft. A vertical incision caudal to the circular scar was used by Kon[29] to expose the glans and penile shaft which was in a subcutaneous position, tightly adherent to the surrounding tissue. Nearly complete direct skin coverage was achieved, apart from a small ventral defect, which was covered by rotation of the scrotal skin. A vertical incision was used also by Byars and Trier[23], and, while Shulman *et al.*[25] did not state the incision employed, both required the use of skin grafts for coverage of the penile shaft. More recently, Radhakrishnan and Reyes[30] chose to use opposing U shaped incisions and so doing were able to obtain skin coverage with vascularized flaps; they contend that the functional and cosmetic results are superior to those of reconstruction with split-thickness grafts, which may result in comparatively inelastic skin on the penile shaft.

Many other forms of surgical mishap have been reported. Laceration to the penile skin and scrotum resulting in exposure of both testes as reported by Shulman *et al.*[25] was managed by primary suturing. Laceration of the penile shaft with resultant partial amputation has also been described[23]. Total ablation of the penis may occur as a result of diathermy injury[31] and loss of the penis from the use of a rubber band as a tourniquet has been reported[32]. Injury to the glans may result from inadequate separation of preputial adhesions. Glandular injury may be of varying severity and cases of complete surgical amputation of the glans have occurred[25]. McGowan[33] described a case in which inadvertent placement of scissors into the urethra while attempting a dorsal slit resulted in surgical bivalving of the glans.

Non-operative complications

Ruff *et al.*[34] described a case of myocardial injury following immediate postnatal circumcision. This was confirmed by a raised level of type MB creatine kinase and by left ventricular posterior wall hypokinesis on echocardiography. It was concluded that the exposure of the child to cold stress as a result of circumcision resulted in a persistent fetal circulation and hypothermia. The neonate had a satisfactory outcome on medical management. A case of recurrent pneumothorax following circumcision was reported by Auerbach and Scanlon[35] in a neonate. The circumcision was complicated by moderate bleeding and the baby's distress was sufficient to produce circumoral cyanosis and persistent tachycardia. It was concluded that crying, induced by the many dressing changes needed to obtain haemostasis, resulted in raised intrapulmonary pressure sufficient to rupture a weak site and cause pneumothorax. Although the child was managed successfully, this required a further hospital stay of 19 days.

Bleeding

Bleeding remains the commonest complication encountered during and after circumcision. Because varying criteria have been used when recording this complication and because of inadequacies in documentation, the reported incidence ranges from 0·1 to 35 per cent[3,12,24,25]. In the majority of cases bleeding is minor and all that is required to achieve haemostasis is gentle pressure on the area. Excessive bleeding may be due to anomalous vessels[25] or the presence of a bleeding disorder[24]. After 13 000 circumcisions reported in two large series, no patient required blood transfusion for bleeding[24,25]. In the event of a bleeding disorder, appropriate clotting factors may have to be administered[24]. The authors are not aware of any reported cases of exsanguination following circumcision.

In some instances the application of pressure alone is insufficient to control local haemorrhage and other methods of haemostasis must be employed. In the UK the commonest aid to haemostasis is electrosurgical diathermy for coagulating vessels. While in the majority of situations the judicious use of this device is safe and effective, the potential for damage exists if it is employed overzealously. When used in monopolar form, an electrical current flows from the indifferent electrode (plate) to the active electrode (forceps) and the tissue surrounding the forceps is heated, resulting in coagulation. However, this coagulation process may spread proximally in small vessels (a phenomenon commonly observed in everyday practice) and the extent of vessel coagulation may be far greater than anticipated or intended. It is predominantly for this reason that the present authors use only *bipolar* diathermy during circumcision. Although there are probably many undocumented cases of minor diathermy burns and sloughing of the affected penile skin, more severe injuries such as glans and major penile skin necrosis have been reported[22,27]. At its most severe, the use of diathermy may result in total ablation of the penis. Gearhart and Rock[31] described four such cases in which damage was so severe that plastic surgical reconstruction was deemed impossible. In all cases the children were managed by gender reassignment and feminizing genitoplasty.

If simple application of pressure is unsuccessful, a type of circumferential bandage may be applied to aid haemostasis. This appears to be popular among the practitioners of religious circumcision in Jewish communities. It may cause a degree of urethral obstruction which, in severe cases, leads to urinary retention[36] and may thus predispose to urinary tract infection[37]. Horowitz *et al.*[38] described such an event in which an 18-day-old infant presented shocked, dehydrated and with a hugely distended abdomen 2 days after circumcision. The tip of the penis, which was still covered by a circular bandage, appeared red and necrotic. After the bandage was released the child voided a large volume of urine and the abdominal distension disappeared. The cause of systemic upset was an *Escherichia coli* urinary tract infection and subsequent septicaemia. Frand *et al.*[39] described an infant about whom the parents were concerned because of bluish discoloration of the legs 1 day after circumcision; a circular bandage was seen around the penis. After this was removed a large volume of urine was voided and the lower-limb cyanosis rapidly disappeared. It is presumed that the distended bladder compresssed the iliac veins and so impeded venous return from the legs. Acute urinary retention may also be caused by the devices sometimes used for circumcision; in one case where the Plastibell device (Abbott Laboratories, Queenborough, UK) was employed, rupture of the bladder was a consequence of acute urinary retention[40]. As well as compressing the urethra, the blood flow to the distal penis and glans may also be compromised by the tourniquet action of a circumferential dressing, which in severe cases may result in necrosis of the distal penis and glans[41].

Pharmacological agents may also be used to stop minor troublesome bleeding and in this respect the application of 1:100 000 adrenaline solution is not uncommon. Although there is a slight danger from systemic absorption, at this low concentration complications are unlikely. If a more concentrated solution is used, however, there is greater systemic absorption with its attendant problems. Mor *et al.*[42] described four such cases in which a sponge-soaked solution of 1:1000 adrenaline had been applied to the circumcision wound and left in place for a few hours. All the children developed tachycardia and heart failure but were successfully managed with digoxin and diuretics. Denton *et al.*[43] reported a similar case of a neonate in whom 0·1 ml of 1:1000 adrenaline was sprayed on to the bleeding area of the frenulum after circumcision. The patient developed tachycardia, acrocyanosis and local pallor of the penis. After subcutaneous injection of phentolamine (an α-adrenergic receptor antagonist) at the base, shaft and corona of the penis, all penile pallor disappeared and the systemic signs abated.

As an alternative to diathermy, obvious bleeding vessels may be ligated with a fine suture. One of the commonest sites for persistent bleeding is at the frenulum, and in this area it is not uncommon to insert a haemostatic suture. However, because of the close proximity of the underlying urethra, it is easy for such a haemostatic stitch to be placed in the urethra itself. The result is the development of a urinary fistula[44,45]. Avoidance of this complication therefore depends on meticulous technique when suturing around the frenulum and in taking superficial tissue only in the stitch.

Sepsis

Infection occurs after circumcision in up to 10 per cent of patients[3,15]. In the majority of cases this is usually mild and manifested by local inflammatory changes, but occasionally there is ulceration and suppuration. Most infections are of little consequence and settle with local treatment. Occasionally, however, sepsis may have much more alarming consequences and may even cause death[46–48].

The perineal skin is heavily colonized by both normal skin saprophytes and by bowel flora, and it is surprising that significant septic complications do not occur more frequently. Woodside[49,50] reported a case of necrotizing fasciitis of the perineum after Plastibell circumcision in a neonate. The child was septicaemic and there was also bacterial contamination of the cerebrospinal fluid. Extensive surgical debridement of the perineum with multiple fasciotomy was necessary and parenteral antibiotics were administered. *Staphylococcus aureus*, *S. epidermidis*, diphtheroids, α-haemolytic streptococcus and *Clostridium perfringens* were cultured from the excised perineal and penile skin. The child survived and had a satisfactory cosmetic and functional result some years later.

Gangrene of the penis has also been reported following circumcision[51] and the scope of microbial contamination of the perineal skin can be further appreciated from the report of Sussman *et al.*[52] of two cases of Fournier's syndrome of the perineum and scrotum following the operation. Both patients survived after adequate antibiotic management, although extensive surgical debridement was necessary in one child. Annunziato and Goldblum[53] presented three cases of staphylococcal scalded skin syndrome all of which occurred after circumcision and, similarly, cases of impetigo have been documented[54]. In 1935, Gosden[47] reported a series of 23 boys from Cyprus circumcised by an unqualified practitioner in 13 of whom tetanus developed; five died. Diphtheria may develop in a circumcision wound[55] and infection with *Mycobacterium tuberculosis* has been documented[18]. The circumcision site has been observed to be the portal of entry in many other cases of sepsis, and Cleary and Kohl[56] reported a fatal case of septicaemia with group B β-haemolytic streptococcus in a 6-week-old child. Kirkpatrick and Eitzman[57] highlighted the significance and occurrence of septicaemia following circumcision with the Plastibell device. Metastatic infection from the circumcision site has been reported as a cause of neonatal meningitis in five children[58,59], three of whom were treated successfully with no long-term sequelae. However, one child subsequently developed cerebral palsy and one died. Osteomyelitis of the femur[25] and a fatal case of staphylococcal bronchopneumonia[60] have also been reported following circumcision. Recently, Crowley and Kesner[48] reported a 9 per cent mortality rate in a series of 45 consecutive admissions for septic complications following ritual circumcision in young adults. Septic embolization and polyarthritis were among the documented complications of septic circumcision in this series. Despite its apparently low incidence, sepsis following circumcision has the potential to cause significant morbidity and in some cases death.

Fistula

Urethrocutaneous fistula following circumcision may occur for a variety of reasons but, fortunately, the reported incidence of this complication is low. Perhaps the commonest cause is a poorly placed suture at the frenulum in an attempt to obtain haemostasis[44,45]. This results in strangulation and necrosis of part of the urethral wall, with resultant subglandular fistulation not dissimilar to glandular hypospadias. Fistulation may also occur as a result of sepsis[61] or unrecognized rare penile anomaly, such as megalourethra[62]. However, many other fistulas arise from using the Plastibell device or Gomco clamp[12,44]. Although the mechanism of injury is not clear it is probable that urethral injury results from crushing by the device. Most of these fistulas open on to the dorsum of the penis (but they may also open to the ventral surface), an anatomical arrangement not dissimilar to that seen in epispadias. Such a case was reported following surgical bivalving of the glans[33]. Although there are many approaches to the management of such a urethral fistula[63], appraisal of the techniques employed is beyond the scope of this review.

Meatal stenosis

Meatal stenosis is generally a direct consequence of circumcision that is seldom encountered in uncircumcised men; meatal calibre is known to be greater in uncircumcised individuals. The incidence of meatal ulceration following circumcision is from 8 to 20 per cent[14,46,64]. The aetiology is thought to be irritation of the external urethral meatus by ammoniacal substances present in wet sodden nappies. Such irritation is unlikely in the presence of a normal prepuce, which serves to protect the glans from these irritant substances[46]. In a prospective study of 140 consecutive neonatal circumcisions, Mackenzie[64] found a 20 per cent incidence of meatal ulceration within the first 2–3 weeks after circumcision. It is thought that meatal ulceration after circumcision is the initiating event in a vicious cycle of stenosis and ulceration, followed by more stenosis[64]. Meatal stenosis following circumcision has been advanced as a cause of recurrent pyelonephritis and obstructive uropathy, for which meatotomy is curative[64,65].

Miscellaneous complications

The glandular epithelium may be denuded by a less than gentle technique when separating the preputial adhesions and this may be exacerbated if the glans is held firmly by a gauze swab. The glans may then be more prone to local sepsis with the resulting formation of a scab. Fortunately, most settle spontaneously with attention to hygiene. A skin bridge may develop between the glans and the penile shaft. This may tether the erect penis so producing pain and deformity. The aetiology of this condition remains unknown, although injury to the glans at the time of circumcision or incomplete separation of the inner preputial skin have been advanced as possible factors[12,66]. Inclusion cysts following circumcision have been described. That reported by Shulman *et al.*[25] was found histologically to be an epidermal cyst. It is possible that cysts also arise as a result of peroperative implantation of smegma. The use of silica talc on surgical gloves has been associated with the formation of granulomas and such a lesion was described in a circumcision wound 15 years after the original surgical procedure[67]. Although penile lymphoedema following circumcision has been reported, there is a paucity of information regarding the aetiology and management of such a problem and accounts in the literature are anecdotal[12,25]. The degree of penile oedema may be greater with the Plastibell device[68]. Impotence has been observed following circumcision[69]. Palmer and Link[70] described two cases, both of which were associated with injection of 1 per cent lignocaine directly into the corpora after application of a rubber band at the base of the penis to act as a tourniquet. As 10–15 ml anaesthetic was used this perhaps resulted in a 50 per cent mixture of lignocaine and blood in direct contact with the vascular endothelium of the penis. It is postulated that this high concentration irreversibly damaged the endothelium of the corpora cavernosum with resulting impotence. Impotence followed partial amputation of the penis at circumcision, despite plastic surgical reconstruction, in a case reported by Hanash[71]. Hypospadias remains a contraindication to circumcision, as surgical reconstruction may require the use of all the available penile skin. However, circumcision in unrecognized hypospadias was performed in six children in one series and, in the same series, although hypospadias was recognized in two children, circumcision was performed anyway[24].

Carcinoma

Of 1103 patients with carcinoma of the penis reviewed by Wolbarst[72], none had been circumcised. It was therefore concluded that squamous carcinoma of the penis only ever occurs in uncircumcised men and that the circumcised state is protective against its development. However, squamous cell carcinoma of the circumcised penis has since been reported[73,74] and so the original contention of a protective effect of circumcision is not convincing. Indeed, when one compares the incidence of carcinoma of the penis in the USA (0–2·1 per 100 000) where most men have been circumcised at birth, with that in Denmark (1·1 per 100 000) and Japan (0·3 per 100 000), where circumcision is rarely performed, the original contention seems doubtful[5,75]. It is likely that several factors other than circumcision are implicated in the genesis of carcinoma of the penis.

Carcinoma of the penis following circumcision appears to have a different natural history from cancer in uncircumcised men. Whereas penile cancer in the uncircumcised tends to arise on the glans or prepuce, after circumcision the tumour is likely to develop in the surgical scar. Such tumours occur mostly on the penile shaft and tend to spread locally with distant metastasis as an infrequent or late occurrence[76]. Surgical excision is the treatment of choice, as neither radiotherapy nor chemotherapy appears to be effective[77]. Nearly all of these cases have been reported from Saudi Arabia, where there existed a radical form of circumcision that was practised by the tribes in the southern regions. The circumcision included excision of the skin in the suprapubic region with a longitudinal incision extending between the anterior superior iliac spines[78]. This practice is now prohibited.

Psychological complications

According to Freudian theory, by the fourth or fifth year of life the genital concentration of all sexual excitement is achieved and the boy's interest in the genitals attains a dominant significance, the phallic stage. Anna Freud[79] wrote:

> 'any surgical interference with the child's body may serve as a focal point for the activation, reactivation, grouping and rationalisation of ideas of being attacked, overwhelmed and (or) castrated'.

For a child at the phallic stage this fear that something might happen to his prized organ is called 'castration anxiety'. According to the psychoanalytical literature, operations performed on the penis, such as circumcision, may arouse such castration fears. In a study on circumcision and the problems of bisexuality, Nunberg[80] highlighted the point that injury to the penis may intimidate the child and impair his development to full virility. However, in the same paper he also proposed that circumcision may stimulate the masculine striving of the child by encouraging identification with the father. After a detailed prospective psychoanalytical study of 12 boys aged 4–7 years undergoing circumcision in Turkey, Cansever[81] found that following surgery there was a significant fall in intelligence quotient and that body image perception showed a tendency to contract. She concluded that:

> 'circumcision is perceived by the child as an aggressive attack upon his body, which damaged, mutilated, and in some cases totally destroyed him. The feeling of "I am now castrated" seems to prevail in the psychic world of the child. As a result he feels inadequate, helpless and functions less efficiently'.

Such psychological sequelae are not confined to the young child. Circumcision performed in the neonatal period is associated with marked behavioural changes[82,83] that may last up to 24 h; supporting this observation is the finding of a rise in both serum cortisol and cortisone levels after neonatal circumcision[84]. Circumcision in the neonate has been noted to increase both respiration and heart rate and is associated with a significant fall in transcutaneous oxygen tension[85]. Allied to this is a change in sleep pattern with prolonged non-rapid eye movement sleep. This change has been interpreted as 'being consistent with a theory of conservation–withdrawal to stressful stimulation'[86].

Circumcision can cause dysmorphophobia, and Walter and Streimer[87] reported a case of genital self-mutilation in a non-psychotic patient who attempted to reconstruct the foreskin himself. Two groups of men seeking restoration of the foreskin have been identified. First is a group of Jewish men who sought to disguise their religious identity during times of political crisis[88]. Second is a group of homosexuals whose circumcised status is associated with unwanted masculinity and anger over having no choice over their circumcision[89]. Genital self-mutilation by attempted circumcision has been reported after paternal death in two patients, both of whom demonstrated features of acute psychosis[90]. Schizophrenia following elective circumcision has also been reported[91].

In societies in which circumcision is intricately linked to tradition and culture, the uncircumcised individual is likely to be an outcast. This prejudice may be great enough for uncircumcised men not only to be ostracized by their peers but even to be attacked and beaten for their lack of conformity. Such beatings in men refusing to be circumcised have occurred in the Xhosa tribe of South Africa and, in one instance, the attack was violent enough to result in the development of 'crush syndrome'[48].

Sexual complications

Morgan[92] asserts that:

> 'penetration in the circumcised man has been compared to thrusting the foot into a sock held open at the top while, on the other hand, in the intact counterpart it has been likened to slipping the foot into a sock that has been previously rolled up'.

He also suggests that 'coitus without a foreskin is comparable to viewing a Renoir whilst colour blind'[93]. While it is impossible to reach an objective conclusion in this matter, some have risen to the challenge[94] and attempted to investigate the question. Although Harnes[95] concluded that 'the question remains unanswered' at the end of his study, the description of his methodology and findings makes for compulsive reading.

Conclusion

Many medical practitioners regard circumcision as a relatively minor procedure and, as such, it is likely to be delegated to a junior surgeon. It has already been observed that complication rate is directly related to operator inexperience[3]. Delegation to a junior colleague should occur only after the surgeon in training has been fully instructed in the operative procedure. Heightened awareness of the scope and potential for complications will of itself result in a reduced complication rate.

Despite the recommendation of the British Medical Association that circumcision should be performed only for medical reasons, controversy still exists over whether too many procedures are being carried out. It is hoped that a greater awareness of the incidence and scope of associated complications will encourage a more carefully considered decision on whether or not to circumcise.

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Infrainguinal revascularization in the diabetic patient

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This article reviews the epidemiological, anatomical and physiological background to infrainguinal arterial reconstruction in the diabetic patient. There is no firm evidence in the literature for the existence of a surgically significant occlusive 'small-vessel' disease in diabetic patients, either as an aetiological component in the pathogenesis of diabetic foot lesions or as a factor limiting the success of infrainguinal bypass grafting. Recent published results of infrainguinal vascular reconstruction in patients with diabetes are reviewed. These are encouraging; early aggressive treatment of lower-limb occlusive disease may be warranted in the diabetic patient.

Peripheral vascular, cerebrovascular and cardiovascular disease are more common in diabetics than in the normal population[1]. In the Framingham study[2] the age-adjusted incidence of intermittent claudication in diabetics was 12·6 per 1000 men and 8·4 per 1000 women; for non-diabetics the corresponding figures were 3·3 and 1·3 respectively[2]. A prospective study using Doppler ankle: brachial arterial pressure ratios has also shown that occult peripheral arterial disease is much more common in patients with type II non-insulin controlled diabetes than in unaffected controls; 22 per cent of diabetics had occult disease compared with only 3 per cent of controls[3]. Type II diabetes mellitus, which is present in 90 per cent of diabetics, carries a sevenfold to 20-fold increase in the incidence of lower-limb arterial occlusive disease[4]. The associated risk factors include raised plasma triglyceride levels, reduced plasma concentrations of high-density lipoproteins, hypertension and increased systolic blood pressure[3]. It is worth noting that the progression of atherosclerotic occlusive disease is relatively rapid in diabetics, which suggests that such patients with symptomatic disease might benefit from aggressive treatment at an early stage[5].

The amputation rate has been suggested as an 'outcome' performance indicator[6]. Between 35 and 45 per cent of all lower-limb amputations are carried out on diabetic patients, although not solely for peripheral vascular disease; standard of footcare[7], age and patient education[8] are the most important preventative factors[9,10]. In the USA, diabetic foot problems are the commonest indication for hospital admission in diabetics[11]. Patients with diabetes may account for 50–70 per cent of all non-traumatic amputations, a figure of some significance when it is appreciated that they make up only 2 per cent of the population[12–14]. These figures represent between 20 000 and 30 000 amputations[15] per year at an estimated cost[16] of US$ 200 million for 1980. The risk of amputation for a diabetic patient is between 15 and 70 times that for a non-diabetic[17,18]. Peripheral vascular disease is the costliest complication of diabetes mellitus in terms of inpatient bed usage[19,20] and in the USA accounts for 1·2 per cent of all hospital costs[21].

Anatomy and pathophysiology

In 1984, LoGerfo and Coffman[22] conducted a literature review of macrovascular and microvascular disease in diabetics. They highlighted the widespread misconception that patients with diabetes mellitus have arteriolar occlusive disease as an aetiological cause of lower-limb ischaemic lesions. This popular misconception stems from the 1959 report by Goldenberg and colleagues[23], who described the presence of periodic acid Schiff-positive material in the arterioles of diabetics; this was interpreted as a specific arteriolosclerosis associated with diabetes mellitus. It is important to recognize, however, that subsequent studies using the Goldenberg technique[24], arterial microcasting[25] down to 10 μm, plethysmographically derived pressure–flow relationships[26] and blood flow response to papaverine[27] have failed to confirm the presence of such lesions. As long ago as 1971, Barner and colleagues[27] concluded that vascular reactivity is not impaired and arterial reconstruction should not be withheld on the basis of arteriolar–capillary involvement in diabetics. Furthermore, the calcification of diabetic vessels is not associated with occlusive disease[28]. There is no evidence[29] for the 'endothelial proliferation' also reported by Goldenberg *et al.*[23]. Although abnormalities of microcirculatory physiology do exist, these are all of a non-occlusive nature. The capillary basement membrane is thicker in diabetics, with a reduced charge resulting from non-enzymatic glycosylation and decreased sulphonation of basement membrane components[30]. This may account for highly charged molecules such as albumin diffusing more readily across the capillary basement membrane[31]. The altered permeability may contribute to an altered cellular nutrition in the diabetic foot. Capillary basement membrane thickening in diabetics is actually associated with an increased luminal capillary diameter[32]. Nevertheless, there is no evidence of an altered diffusion of oxygen; indeed, it has been shown that the transcutaneous partial pressure of oxygen in the ulcerated diabetic foot is frequently raised above normal[33]. The situation is complex in that capillary pressure within the diabetic foot is abnormally high[34], but laser Doppler ultrasonographic studies have shown a reduction of cutaneous microvascular blood flow, volume and erythrocyte velocity, particularly in the lower limb[35], suggesting that there is an impairment of skin blood flow. There is no distal predominance of this abnormality, which suggests that its cause is not neuropathic. The explanation for these changes may be deep cutaneous capillary loss, increased capillary resistance or selective loss of arteriovenous shunts.

The distribution of macrovascular occlusive disease in diabetic patients differs from that in non-diabetics. Conrad[25] used amputation specimens to demonstrate that occlusive atherosclerosis in diabetes tends to involve the infrageniculate arteries between the knee and ankle, sparing the foot. Strandness *et al.*[24] confirmed this as the major site of atherosclerosis and also showed that the foot vessels of diabetics are not dramatically different from those of non-diabetics in terms of sparing by atherosclerosis. Strandness also found that the dorsalis pedis artery was spared in about 70 per cent of both diabetic and non-diabetic individuals; a more recent angiographic study confirmed this observation[36].

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Evaluation

Diabetics with peripheral vascular disease are at greater risk of the more severe manifestations of ischaemia, such as rest pain, ulceration and gangrene, than non-diabetics[37,38]. A principal reason for this is that the lower limb of the patient with diabetes is often affected not only by vascular disease but also by peripheral neuropathy. The overall effect is that a high arterial perfusion pressure is required to prevent ulceration and small areas of gangrene; these lesions may occur in the presence of relatively mild ischaemia in the diabetic patient. While this should be kept in mind when evaluating the diabetic, the single most important step in assessment of infrainguinal vascular disease is the same as in the non-diabetic patient, namely the examination of peripheral pulses. Although diabetic individuals have a greater propensity to develop occlusive tibial artery disease, the superficial femoral artery is still the commonest site of arterial occlusion[39].

Non-invasive investigation using a hand-held Doppler ultrasonographic probe to detect opening pressure is affected by the presence of medial calcinosis in the arteries of patients with diabetes. This may raise the luminal opening pressure by about 25 mmHg over that found in the non-diabetic patient with the same infrainguinal arterial pressure; in some diabetics it may be impossible to obliterate the Doppler signal[40,41]. The critical level of pressure associated with healing of foot ulceration in diabetics is higher than in non-diabetics[42]; this is possibly the product of this occlusion artefact. The difficulty caused by the unobliterable signal may be overcome by using toe digital artery opening pressure[43]. Measurement of the transcutaneous partial pressure of oxygen is not reliable in diabetics with ulceration; such patients frequently have a higher oxygen tension than non-diabetics with ulcers, and amputation wounds and ulcers may fail to heal at levels of oxygenation that would be adequate in non-diabetic patients[33]. A more recent report claimed a greater predictive value for transcutaneous partial oxygen pressure measurement if both supine and elevated readings are made[44]. Although clinical examination is important, it has been recommended that in a small number of cases angiography may still be appropriate despite palpable foot pulses[45].

Modern digital subtraction angiography (DSA) allows good imaging of small-bore distal vessels, which standard angiography may fail to outline[46,47]. Concern has been raised about contrast agent-induced renal failure in the diabetic patient, but there appears to be no increased incidence of such renal failure in diabetics with normal renal function[48]. However, the risk of developing renal failure in the presence of renal insufficiency has been reported to be as high as 41 per cent[49]; it is important to maintain adequate renal output before, during and after angiography by the use of diuretics[50], hydration or both[51]. The nephrotoxicity of contrast agent is related to its hypertonicity following dissociation into two ions[52], possibly due to morphological changes in the red blood cells causing microvascular obstruction[53], and a direct toxic effect on the renal cell[54]. Other possible causes of nephrotoxicity are related to protein tubular obstruction[55], urate nephropathy secondary to a uricosuric effect of contrast agent[56], and antibodies to contrast agent causing antigen–antibody complex deposition or renal cell cross-reactivity[57]. The nephrotoxic effect appears to be dose related (measured in grams of iodine), with 80–90 g iodine being the approximate dose at which the risk of renal failure increases significantly[58]. The development of non-ionic contrast agents, which do not dissociate, has reduced the incidence of renal failure following angiography[59,60]. DSA, in which computer enhancement of images allows the use of smaller doses of contrast agent, has been heralded as a better method of visualizing the distal vessels of the leg[61,62], although some have expressed concern about the clarity of the final image[63].

Clinical results

It is widely believed that operative risk is greater in diabetic than non-diabetic patients undergoing infrainguinal revascularization. Diabetics have a greater incidence of coronary artery disease, hypertension and renal insufficiency. Nevertheless, the incidences of previous myocardial infarction and cerebrovascular accident have been shown to be virtually the same in the diabetic and non-diabetic populations at the time of vascular reconstruction; approximately 40 per cent of patients have had a myocardial infarction and 12 per cent a stroke[38,64].

In the 1970s it was suggested that the diabetic with limb-threatening ischaemia was not a good candidate for revascularization[65,66]. What of more recent results specifically related to vascular reconstruction? Comparison of 5-year patency rates for infrainguinal bypass grafting in a single institution showed a favourable result in the diabetic population; a patency rate of 62 per cent was achieved in 95 diabetics compared with 52 per cent in 72 non-diabetics, with good rates of utilization of vein, 94 and 76 per cent respectively[64]. A further comparison of 75 diabetic and 75 non-diabetic patients undergoing infrainguinal bypass (approximately 80 per cent to below the knee joint in both groups but with significantly more to tibial and pedal vessels in the diabetics) demonstrated 1- and 4-year patency rates of 95 and 89 per cent respectively in the diabetic group compared with 85 and 80 per cent in the non-diabetics[67]. The largest study available, comparing 387 diabetics and 294 non-diabetics receiving tibial artery bypass grafts, showed 1- and 5-year patency rates of 91 and 74 per cent in patients with diabetes, compared with 90 and 76 per cent in those without[68]. These reports are summarized in *Table 1*. The most recent study dealing with this type of comparison was reported in 1992; it did not give patency data for individual groups but reported an overall 3-year primary patency rate of 58 per cent, stating that no statistically significant difference existed between results for insulin-controlled diabetics, non-insulin controlled diabetics and non-diabetics[38]. It is also worth recording the results of an aggressive revascularization policy towards juvenile-onset diabetes mellitus (type I) from the New England Deaconess Hospital, Boston; a 2-year primary vein graft patency rate of 83 per cent was achieved, with 16 per cent of the study group dying within this period[69].

Infrainguinal bypass, the origin of which is distal to the common femoral artery, has been regarded by many as only a compromise procedure, for use when insufficient length of vein is available[70,71]. It is important to appreciate, however, that the distribution of atheromatous disease in patients with diabetes mellitus is typically tibioperoneal. It is not uncommon to find ischaemic foot lesions in the presence of a palpable

Table 1 *Primary patency rates of infrainguinal bypass grafting for diabetic and non-diabetic patients*

		Non-diabetics			Diabetics		
Reference	Year	1 year	4 years	5 years	1 year	4 years	5 years
Hurley *et al.*[64]	1987	—	—	52	—	—	62
Shah *et al.*[68]	1988	90	—	76	91	—	74
Rosenblatt *et al.*[67]	1990	85	80	—	95	89	—

Values are percentages

popliteal pulse and the popliteal artery may frequently provide a suitable site of origin for a bypass graft. Diabetics may have both spared and stable inflow and outflow tracts, which may optimize the results of popliteal–distal vessel bypass. In 1981, Veith and colleagues[72] reported acceptable results following use of the distal superficial femoral or popliteal artery as an inflow site. Only 3 per cent (one graft) of their series possibly occluded because of progression of more proximal disease. Stonebridge and colleagues[73], in a series of 124 popliteal–distal bypass grafts, reported 1- and 3-year primary patency rates of 89 and 85 per cent, with a perioperative mortality rate of 0·8 per cent. Similar results have been reported by others[74–79] (*Table 2*). A significant advantage of such a manoeuvre is that the graft length is shortened. Ascer and colleagues[80] showed in a non-randomized retrospective study that there is a statistically significant advantage in terms of patency rate for short over long vein grafts, especially in the presence of poor run-off. Shorter grafts also facilitate use of alternative conduits such as arm vein and short saphenous vein[81].

Budd and colleagues[82] on simple analysis suggested that diabetes was a significant adverse risk factor for graft patency; however, when proportional hazards analysis was performed diabetes no longer appeared significant. In contrast, Rutherford and colleagues[83], in an analysis of factors affecting graft patency, showed a significant advantage for diabetic patients.

How far distally can one insert a bypass graft and hope for success? Pomposelli and colleagues[84], in a series of patients containing 94 per cent with diabetes, reported 97 bypasses to the dorsalis pedis artery, using the femoral artery as the graft origin in 50 per cent and the popliteal artery in the remainder. There was an 18-month graft patency rate of 82 per cent; limb salvage and patient survival rates at 18 months were 87 and 80 per cent respectively. Twelve dorsalis pedis arteries in this series were explored despite not being imaged on preoperative DSA; six were found to be satisfactory for the insertion of a bypass graft. Harrington and colleagues[85] also reported a series of patients with bypass to the dorsalis pedis artery that included 78 per cent diabetics. Some 73 bypasses were carried out with a 2-year graft patency rate of 59 per cent. Failure was attributed to poor vein quality, continuing foot infection and skin incision necrosis. Andros and colleagues[86] reported the results of bypass grafts to 20 lateral plantar arteries; there were 16 diabetic patients in the series. Ten bypasses originated from the popliteal artery, four from the common femoral artery and six from previous grafts. The patency rates documented only at 1 and 3 months were 85 and 73 per cent respectively. A summary of the results of infrainguinal bypass in diabetic patients over the past 5 years is given in *Table 3*. This shows a range for 1- and 3-year patency rates of 71–94 per cent and 56–88 per cent respectively.

Table 2 *Primary patency rates of infrainguinal bypass grafts originating from the popliteal artery*

Reference	Year	No.	Diabetics (%)	Patency rate (%) 1 year	Patency rate (%) 3 years
Veith *et al.*[72]	1981	24	71	82	82
Schuler *et al.*[75]	1983	23	71	84	84
Sidawy *et al.*[77]	1986	29	74	81	81
Cantelmo *et al.*[74]	1986	32	74	79	79
Rhodes *et al.*[76]	1987	26	77	95	—
Rosenbloom *et al.*[78]	1988	49	96	83	62
Stonebridge *et al.*[73]	1991	124	100	89	85
Marks *et al.*[79]	1992	32	66	90	85

The problem of calcification in the arteries of diabetic patients has already been mentioned. Medial calcification, shown radiologically, occurs twice as commonly in diabetics as in non-diabetics[23] and such calcification might be thought to be detrimental to vascular reconstruction. The question has, however, rarely been addressed. Ascer and colleagues[87] described no statistically significant difference between the long-term patency rates of grafts to circumferentially calcified ($n = 36$), partially calcified ($n = 203$) and non-calcified ($n = 116$) tibial vessels; the respective 3-year patency rates were 47, 58 and 45 per cent. They concluded that 'arterial calcification is an invalid predictor of failure in small vessel bypasses'. This view was supported by results from a smaller series of patients with calcified distal arteries, for whom the 3-year graft patency rate did not differ from that after bypass to non-calcified vessels[88].

The other main local problem associated with diabetic peripheral vascular disease is the concurrent presence of foot sepsis and ischaemia. While such sepsis may delay surgery because of the need for local debridement or amputation (although certain centres report no difference in this respect between diabetic and non-diabetic patients[64]) and may increase the length of hospital stay after operation, the 3-year patency rate for bypass grafts in such situations may be as high as 92 per cent, with a corresponding 96 per cent limb salvage rate[89]. Rubin and colleagues[90] compared reconstruction to the tibial arteries in the presence and absence of pedal sepsis. Not only was there a greater proportion of diabetics than non-diabetics in the group with sepsis, 74 *versus* 44 per cent, there was also a greater proportion of smokers, 85 *versus* 62 per cent. Graft patency data were not recorded but limb salvage rates were not statistically different 3 years after operation: 68 per cent for patients with foot sepsis at the time of surgery *versus* 74 per cent for those without.

In summary, the literature contains few data to suggest that successful infrainguinal bypass is less likely in diabetics than in non-diabetics; rather, the opposite may be true. Several studies have also indicated that early aggressive surgical treatment of lower-limb occlusive arterial disease may be warranted in the diabetic patient. Indeed, it has been claimed that distal arterial reconstruction is a principal factor in reducing the frequency of amputation for ischaemia in diabetic patients[91]. The reported series of such operations from specialist vascular centres describe good results with long-term durability.

Table 3 *Primary patency rates of infrainguinal bypass grafting in populations containing a high percentage of diabetic patients*

Reference	Year	No.	Diabetics (%)	Patency rate (%) 1 year	Patency rate (%) 3 years	Patency rate (%) 5 years	Comments
Andros *et al.*[92]	1988	166	65	94	88	82	To ankle and foot
Pomposelli *et al.*[84]	1990	97	94	—	82*	—	To dorsalis pedis
Klammer *et al.*[93]	1990	68	62	88	68	—	To inframalleolar
Shah *et al.*[94]	1992	270	61	—	—	61	Groin to ankle
Harrington *et al.*[85]	1992	73	78	71	56	—	To dorsalis pedis

*At 18 months

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Smoking impairs endothelium-dependent relaxation of saphenous vein

Samples of proximal saphenous vein were obtained from heavy smokers and non-smokers: 28 were obtained at varicose vein surgery and eight at infrainguinal bypass surgery. The veins were prepared for histological examination and for mounting in an organ bath to measure changes in isometric tension. Vein rings from both smokers and non-smokers responded equally to sodium nitroprusside, a reagent that acts directly on smooth muscle cells, undergoing 90–100 per cent relaxation. The mean(s.e.m.) maximum relaxation in response to bradykinin of rings obtained at varicose vein surgery was 50·0(5·3) per cent in non-smokers compared with only 31·6(2·2) per cent in smokers (P = 0·03). Similarly, in specimens obtained at bypass surgery the mean(s.e.m.) maximum relaxation in smokers was only 25·1(6·3) per cent compared with 48·4(4·1) per cent in smokers (P = 0·04). Relaxation in response to the bradykinin stimulus was abolished in the presence of L-nitroarginine methyl ester, a specific inhibitor of the synthesis of endothelium-derived relaxing factor (EDRF). Preincubation of the vein rings with L-arginine, the precursor of EDRF, did not increase the vasorelaxation in smokers. The mean(s.e.m.) maximum relaxation in response to the calcium ionophore A23187 was 53·5(3·8) per cent in non-smokers compared with only 27·0(4·9) per cent in smokers (P = 0·01). The results indicate that heavy smokers have impaired release of EDRF in response to both bradykinin and calcium ionophore. This impairment may increase vasomotor tone, platelet aggregation and smooth muscle proliferation, thereby resulting in an increased risk of graft occlusion.

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Saphenous vein is the optimum conduit for infrainguinal bypass, especially where the graft crosses the knee[1–3]. Occlusion of vein grafts is a major problem in vascular surgery and may lead to limb loss. Most vein graft occlusions occur within 6–12 months after bypass surgery. A major cause of early failure is the development of intrinsic lesions, which lead to narrowing of the lumen and graft thrombosis[4,5]. Other factors that contribute to graft occlusion include continuation of smoking after bypass surgery and raised levels of plasma fibrinogen[6]. Smoking is considered to damage the endothelium, but no particular studies have been carried out on the effect of smoking on the endothelium of saphenous vein. Vascular endothelium produces two endogenous vasodilators, prostacyclin and endothelium-derived relaxing factor (EDRF). EDRF is now known to be nitric oxide. These two vasodilators also act synergistically to inhibit platelet aggregation and adhesion, processes that could directly promote thrombosis. Smoking has been demonstrated to reduce the production of prostacyclin by cultured vascular endothelial cells[7]. Recently it has been demonstrated that endothelium-dependent regulation of arterial tone is impaired in smokers[8]. In this study, endothelium-dependent relaxation of saphenous vein, which is also impaired in smokers, is reported.

Patients and methods

Segments of proximal long saphenous vein were obtained with minimal trauma from two groups of patients, those undergoing ligation and excision of the long saphenous vein for the correction of varicose veins (28 patients) and those undergoing distal revascularization for critical ischaemia (eight). Preoperative duplex ultrasonography demonstrated competence of the long saphenous system in patients receiving bypass. Smokers were defined as current smokers with at least a 10 pack-year history of smoking. In the varicose vein group, non-smokers were patients who had never smoked; in the vein bypass group, non-smokers were those who had not smoked for at least 5 years. Serum samples were obtained at the time of surgery for estimation of cotinine, the principal stable metabolite of nicotine; cotinine levels >200 nmol/l were considered indicative of current smoking. Patients with diabetes, those receiving antihypertensive or nitrate therapy, and those who had previously had venous thrombosis or venous surgery were excluded from the study. The demographic details of the patients are shown in *Table 1*.

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Table 1 *Demographic details of patients*

	Varicose vein surgery	Distal bypass surgery
Smokers		
No. of patients	13	4
Mean (range) age (years)	48 (39–62)	71 (60–82)
Sex ratio (M:F)	2:11	3:1
Cotinine range (nmol/l)	589–1447	958–1489
Non-smokers		
No. of patients	15	4
Mean (range) age (years)	51 (40–67)	72 (65–78)
Sex ratio (M:F)	4:11	2:2
Cotinine range (nmol/l)	36–106	38–82

Materials

L-arginine, bradykinin acetate, L-nitroarginine methyl ester (L-NAME), calcium ionophore A23187, sodium nitroprusside, indomethacin and L-phenylephrine were all obtained from Sigma Chemicals, St Louis, Missouri, USA. Krebs' Ringer solution contained 118·4 mmol/l NaCl, 4·7 mmol/l KCl, 2·5 mmol/l $CaCl_2$, 1·2 mmol/l $MgSO_4 \cdot 7H_2O$, 24·9 mmol/l $NaHCO_3$, 1·2 mmol/l KH_2PO_4, 11·1 mmol/l glucose and 10 μmol/l indomethacin.

Histological examination

A segment of saphenous vein adjacent to that used for organ-bath studies was fixed in either 10 per cent buffered formalin for light microscopy or in 1 per cent glutaraldehyde for scanning electron microscopy, which was used to confirm that the endothelial cell layer was intact.

Organ-bath studies

The segment of proximal saphenous vein was excised and placed immediately into modified Krebs' solution at 4°C and transported to the laboratory. Excess fat and connective tissue were carefully dissected from the 2-cm segment, and 5-mm vein rings cut and suspended between metal stirrups in the chamber of an organ bath containing 10 ml Krebs' Ringer buffer at 37°C, oxygenated with 95 per cent oxygen mixed with 5 per cent carbon dioxide. The upper stirrup was connected by surgical silk to an isometric type D transducer (Bioscience, Washington, Sheerness, UK) and the lower stirrup to a glass tissue holder. The vein ring was allowed to equilibrate for 60 min, during which time the chamber solution was changed every 15 min. Vein rings were stretched at 0·5-g intervals and exposed to phenylephrine (0·3 μmol/l) at each level of stretch until the optimum length–tension relationship was obtained, usually 2–3 g. After a further 30 min equilibration, a dose–response curve to phenylephrine (10^{-9} to 10^{-4} mol/l) was obtained. The vein ring was then washed thoroughly with Krebs' Ringer solution and allowed to equilibrate for a further 30 min before agonist-induced relaxation. For this, vein rings were exposed to a submaximal dose of phenylephrine and accumulative doses of bradykinin (10^{-9} to 10^{-5} mol/l) or calcium ionophore (10^{-9} to 10^{-5} mol/l), which were added at intervals of 2 min or until a stable response was observed. After each relaxation dose–response curve, the vein rings were again washed thoroughly with Krebs' Ringer solution and a further 30 min equilibration allowed before a new dose–response curve was estimated. For some experiments, vein rings were preincubated with L-NAME (0·1 mmol/l) for 30 min before a dose–response curve was performed. In other circumstances, vein rings from smokers were preincubated with 3 mmol/l L-arginine for 30 min before the dose–response curve was effected.

Results

Serum cotinine levels for the patients are shown in *Table 1*. All those considered as non-smokers had cotinine levels <200 nmol/l and all smokers had levels in excess of this value. Light microscopic examination of vein segments did not reveal gross intimal thickening or damage in any of the specimens used in organ-bath studies. Scanning electron microscopy demonstrated that the endothelium was well preserved with no significant areas of endothelial damage or denudation in the vein specimens (*Figure 1*).

The logarithm of the concentration of phenylephrine required to produce 50 per cent contraction was similar for vein rings from smokers and non-smokers. Sodium nitroprusside bypasses the endothelium and acts on the smooth muscle to produce direct relaxation of vein rings. The mean(s.e.m.) maximum relaxation in response to 10 μmol/l nitroprusside was similar in both groups, 96·4(3·1) per cent in non-smokers (17 patients) and 93·8(5·3) per cent in smokers (19).

The dose–response curves for relaxation in response to bradykinin of the specimens obtained at varicose vein surgery are shown in *Figure 2*. The mean(s.e.m.) maximum relaxation in non-smokers (seven patients) was 50·0(5·3) per cent and that in smokers (nine) 31·6(2·2) per cent ($P = 0{\cdot}03$, Mann–Whitney *U* test). The logarithm of the concentration required to produce 50 per cent of the maximum relaxation (EC_{50}) did not differ significantly between non-smokers and smokers. The dose–response curves for bradykinin-induced relaxation of vein rings obtained at bypass surgery are shown separately in *Figure 3*. Again, the mean(s.e.m.) maximum relaxation in non-smokers (four patients) was significantly greater than that in smokers, 48·4(4·1) and 25·1(6·3) per cent respectively ($P = 0{\cdot}04$, Mann–Whitney *U* test). The EC_{50} for bradykinin was similar for smokers and non-smokers. The shapes of the dose–response curves for the vein rings obtained at bypass surgery are different from those for rings obtained at varicose vein surgery. The

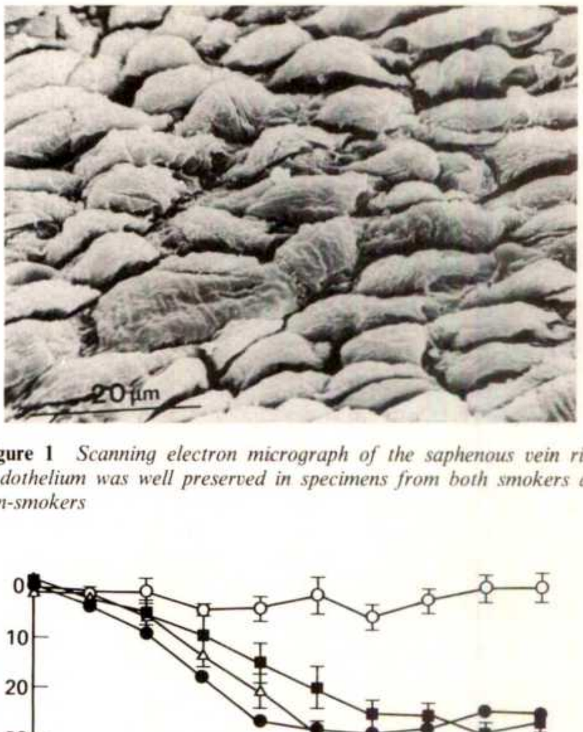

Figure 1 *Scanning electron micrograph of the saphenous vein ring. Endothelium was well preserved in specimens from both smokers and non-smokers*

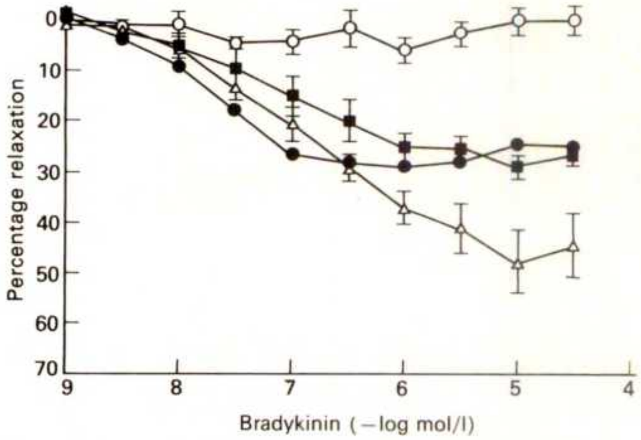

Figure 2 *Cumulative dose–response curves to bradykinin for vein rings obtained at varicose vein surgery. Relaxation is expressed as the percentage decrease in tension of the contraction induced by phenylephrine. Values are mean(s.e.m.). The mean maximum relaxation in non-smokers* (△; n = *7*) *was significantly greater than that in smokers* (■; n = *9*) (P = *0·03, Mann–Whitney* U *test*). *Preincubation of vein rings with 0·1 mmol/l* L*-nitroarginine methyl ester* (○; n = *6*) *abolished the relaxation to bradykinin. Preincubation of vein rings from smokers with 3 mmol/l* L*-arginine* (●; n = *4*) *did not increase the maximum relaxation to bradykinin*

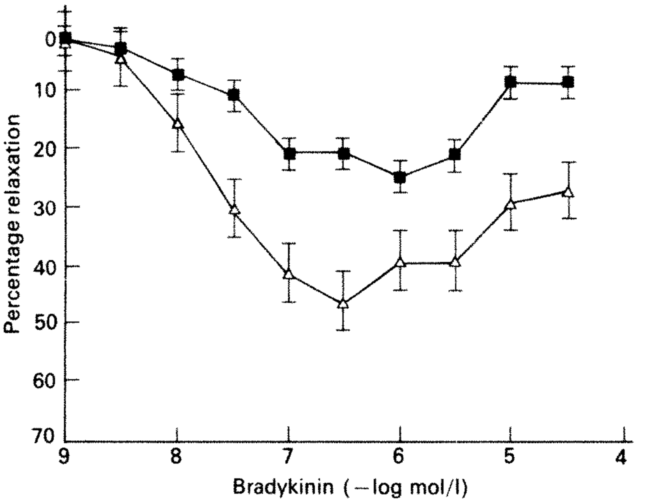

Figure 3 *Cumulative dose–response curves to bradykinin for vein rings obtained at bypass surgery. Relaxation is expressed as the percentage decrease in tension of the contraction induced by phenylephrine. Values are mean(s.e.m.). The mean maximum relaxation in non-smokers* (△; n = *4*) *was significantly greater than that in smokers* (■; n = *4*) (P = *0·04, Mann–Whitney* U *test*)

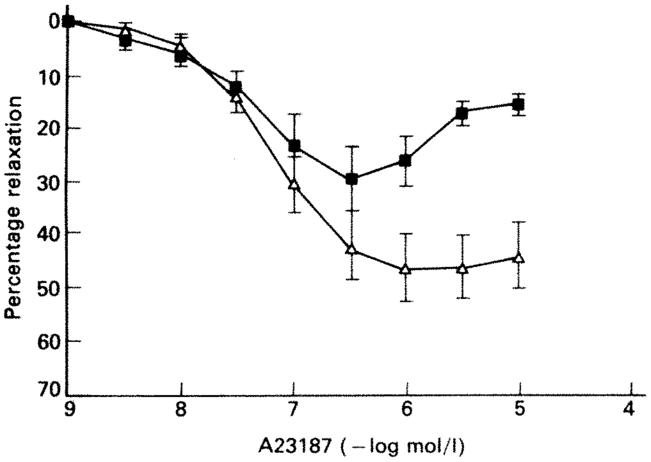

Figure 4 *Cumulative dose–response curves to calcium ionophore A23187 for vein rings obtained at varicose vein surgery. Relaxation is expressed as the percentage decrease in tension of the contraction induced by phenylephrine. Values are mean(s.e.m.). The mean maximum relaxation in non-smokers* (△; n = *6*) *was significantly greater than that of smokers* (■; n = *6*) (P = *0·01, Mann–Whitney* U *test*)

mean(s.e.m.) EC_{50} for bradykinin for bypass veins was significantly lower than that for vein rings obtained at varicose vein surgery: 0·25(0·02) × 10^{-7} mol/l for bypass vein and 1·50(0·02) × 10^{-7} mol/l for varicose vein ($P = 0·03$, Mann–Whitney *U* test). Preincubation of the vein rings from both non-smokers and smokers with L-NAME abolished the relaxation to bradykinin, confirming that the vasorelaxation was being mediated by nitric oxide (*Figure 2*). Preincubation of vein rings from smokers with 3 mmol/l L-arginine did not increase the maximum response to bradykinin (*Figure 2*).

Further experiments investigated the response of vein rings obtained at varicose vein surgery to the calcium ionophore A23187. For rings obtained at varicose vein surgery the mean(s.e.m.) maximum relaxation in response to A23187 was 53·5(3·8) per cent in non-smokers compared with only 27·0(4·9) per cent in smokers ($P = 0·01$, Mann–Whitney *U* test) (*Figure 4*). Similarly, for veins harvested at bypass surgery, the results in response to A23187 were closely similar to those for bradykinin, with increased maximum relaxation in non-smokers compared with smokers (data not shown).

Discussion

The obligatory role of the endothelium in controlling vasomotor tone was first described by Furchgott and Zawadski[9] in 1980. Several years later it was demonstrated that endothelial cells synthesize and secrete EDRF, further characterized as nitric oxide[10,11]. Other important effects of nitric oxide are inhibition of platelet aggregation and adhesion, and reduction of the proliferation of vascular smooth muscle cells in culture[12,13]. Recently, a non-invasive method has been described[8] for the investigation of arterial endothelial cell dysfunction *in vivo*: this involves monitoring the diameters of the brachial and superficial femoral arteries in response to changes in arterial blood flow. The endothelium-dependent relaxation of superficial femoral artery was reduced in smokers, whereas endothelium-independent relaxation, by glyceryl trinitrate, was unaffected[8].

Basal release of nitric oxide is higher in arteries than in veins[14]. Nevertheless, it has been considered[15] that nitric oxide release could have an important role in maintaining the patency of vein bypass grafts. The early success of vein bypass grafting may be short lived since vein graft stenosis and occlusion are major clinical problems. Most vein graft stenoses and occlusions occur within the first year after bypass surgery and it has been advocated[16,17] that all vein grafts should remain under continuous surveillance during this time. The aetiology of vein graft failure has been attributed to the formation of strictures, intimal hyperplasia, thrombosis and progression of distal disease. The risk of vein graft failure is increased in smokers[6]. Some of this increased risk might result from impaired release of nitric oxide from the endothelium of vein grafts, both at the time of grafting and later as the grafts adapt to the arterial circulation.

The similar vasorelaxation of saphenous vein rings of smokers and non-smokers to sodium nitroprusside indicates that smoking does not directly damage the vasomotor responses of the venous smooth muscle cells. This is in agreement with the findings of Celermajer *et al.*[8] for the arterial circulation. Bradykinin effects the synthesis and release of nitric oxide (EDRF) by stimulation of a receptor on the surface of the endothelial cell. The calcium ionophore A23187 bypasses membrane receptors and acts directly to affect intracellular calcium levels and stimulate the synthesis and release of nitric oxide. Both these agonists produced much greater relaxation in the vein rings of non-smokers compared with those of smokers, and relaxation of the vein rings of smokers was not increased by preincubation with L-arginine. The relaxations were blocked by L-NAME, a specific inhibitor of nitric oxide synthesis; all experiments were performed in the presence of indomethacin to inhibit vasoactive prostanoid formation. Therefore, the reduced relaxation in smokers appears to be dependent on nitric oxide, but specifically was not attributable to either a membrane receptor defect or to the depletion of L-arginine, the precursor of nitric oxide.

Most of the studies were performed using proximal saphenous vein harvested at varicose vein surgery. Even in patients with varicose veins, the proximal saphenous vein was minimally dilated and the intima histologically normal. These patients were significantly younger than those undergoing bypass surgery, and the smokers had shorter smoking histories. Similar effects of smoking on bradykinin-induced relaxation were seen in both veins obtained at varicose vein surgery and those from bypass grafting. However, there were differences in the response of the older bypass veins, including a lower EC_{50}, even though the mean maximum relaxation of non-smokers was similar in both groups, as was that of smokers. The similarities provide reassurance that the results of endothelial function in the proximal saphenous vein harvested at varicose vein surgery are also applicable to bypass veins. The patient exclusion criteria strictly limited the number of bypass veins available for investigation. Nevertheless, even with only four patients in each group, there was a clear difference between smokers and non-smokers.

From the present studies it can be concluded that endothelium-dependent relaxation of vein and release of nitric oxide from vein are reduced in smokers. With the knowledge that endothelium-dependent relaxation of the arterial circulation is also impaired in smokers, the reduced vasorelaxation of saphenous vein in smokers is likely to be maintained as the vein graft matures[8]. Since nitric oxide has important influences on two other processes associated with graft failure, platelet aggregation and smooth muscle cell proliferation, the impaired release of nitric oxide in smokers' veins and vein grafts could provide the common underlying mechanism for the increased risk of graft failure in smokers.

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Influence of type III collagen genotype on aortic diameter and disease

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Type III collagen contributes to the tensile strength of the aortic wall, and mutations in the type III collagen gene have been suggested as the basis for the familial tendency to abdominal aortic aneurysm (AAA). Variation in this gene was investigated in 153 patients with AAA, 87 with aortoiliac stenosis and 98 age-matched controls. The rare mutation at amino acid 619 of Gly → Arg, previously associated with AAA in a single family, was not found in any of the patients with aneurysm. For the Ala → Thr variation at amino acid 531, the frequency of the threonine allele was 0·25 in patients with AAA and stenosis, compared with 0·35 in controls. The frequency of the rare allele in the region 3′ to the gene demonstrated by Ava II digestion (0·27 in the general population) was found to be 0·29 in the AAA group and 0·19 in the stenosis group (P = 0·023). In the AAA group the presence of the Ava II rare allele was associated with a significant increase in aneurysm diameter (P = 0·044). Non-invasive assessment of aortic distensibility was available in 25 patients: those carrying the Ava II rare allele had less distensible aortas than those not carrying this allele (median pressure–strain elastic modulus 42·0 and 23·9 N/cm^2 respectively, P = 0·008). Variation in the type III collagen gene may influence the mechanical properties of the ageing aorta and hence its susceptibility to disease and dilatation. In contrast, there is no evidence for a single common founder mutation in type III collagen predisposing to AAA.

Atherosclerosis diffusely affects many arteries. In smokers the disease appears to have a predilection for the abdominal aorta[1]. Other considerations, including flow, mechanical forces and the microanatomy of the aortic wall, are likely to dictate whether a haemodynamically significant stenotic lesion develops in the aortoiliac segment. Similar considerations are likely to influence the development of abdominal aortic aneurysm (AAA). However, there also is strong familial predisposition to AAA, indicating a genetic component[2–4].

Aortic fragility and aortic rupture have been associated with mutations in two of the connective tissue components of the aortic wall: fibrillin in Marfan's syndrome and type III collagen in Ehlers–Danlos type IV disease[5,6]. Also a mutation, Gly → Arg, at position 619 in type III collagen has been associated with AAA in a single family in the USA[7]. Collagen provides great tensile strength. However, in the normal aorta elastin is considered to be a more important load-bearing component[8]. As the aorta ages, stiffens and becomes susceptible to degenerative change, the load-bearing components alter such that collagen becomes more important[8,9]. Although type III collagen comprises only one-third of the aortic media collagen (the remainder being principally type I), it is the more extensile collagen and is, therefore, important in resisting pulse pressure.

In this paper evidence is presented to suggest that variation in the type III collagen gene may influence both the development of disease in the abdominal aorta and, more particularly, the extent of aneurysmal dilatation; it is not confirmed that mutations in type III collagen are a common genetic cause of AAA.

Patients and methods

Patients were recruited consecutively from the Charing Cross Hospital arterial clinic and included 153 with AAA, 87 with haemodynamically significant aortoiliac stenosis resulting in intermittent claudication or Leriche's syndrome, and 98 control subjects with atherosclerotic disease of the carotid artery or peripheral arteries supplying the lower limb (femoropopliteal disease without a significant aortoiliac component). The demographic features of these three groups are given in *Table 1*. The maximum anteroposterior external aortic diameter of all patients was measured using B-mode ultrasonography. Aortoiliac stenosis was assessed by angiography, colour-flow Doppler ultrasonography (Acuson 128; Acuson, Mountain View, California, USA) and segmental pressure decrease in the leg arteries.

For each patient a blood sample was obtained and used for the measurement of cotinine and cholesterol levels, determination of haptoglobin phenotype and for the isolation of genomic DNA. The genomic DNA was assessed for the presence of two polymorphic variations in or close to the type III collagen gene: the variable Ava II site 3′ to the gene, determined by Southern blotting, and the variable Alu I site, associated with an Ala → Thr variation at position 531 of the protein, using a polymerase chain reaction[10,11]. The presence of a Gly → Arg mutation at amino acid 619 was investigated as described previously[7].

In 25 consecutive patients presenting for elective repair of AAA between March and September 1989, the pressure–strain elastic modulus of the dilated abdominal aorta was investigated non-invasively using M-mode ultrasonography[9].

For statistical analysis, the Mann–Whitney *U* test was used to compare non-parametrically distributed variables, the χ^2 test to compare gene allele frequencies and analysis of variance to associate aneurysm diameter with other variables.

Results

The details of the three groups of patients given in *Table 1* include information about diabetes and ischaemic heart disease, angina or previous myocardial infarction, blood pressure and cholesterol measurements. The patients with AAA were significantly older, taller, had a lower incidence of diabetes and were disproportionately male compared with the other two

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groups. The ethnic distribution among the three groups was similar.

The frequency of the allele coding for threonine at position 531 of type III collagen (Alu I polymorphism) was the same, 0·253, in patients with AAA and in those with aortoiliac stenosis. In controls the allele coding for Thr-531 was more common, 0·352 (*Table 2*); the difference between the AAA group and controls was significant (P = 0·040). Polymorphic variation at the Ava II site was determined only in the AAA and stenosis groups: information concerning the frequency of this polymorphism in the general population has been reported previously, with a frequency of 0·27 for the rare allele[10]. The frequency of the rare Ava II allele in the AAA group was 0·288, similar to that in the normal population, but its frequency in the stenosis group was significantly lower, 0·186 (P = 0·023). The presence of a Gly → Arg mutation at amino acid 619 of type III collagen was not detected in any patient (*Table 2*).

In the AAA group there was no association between aneurysm diameter and age, blood pressure, cholesterol level or haptoglobin phenotype. Women had smaller aneurysms than men (median diameter 5·5 *versus* 7·0 cm, P = 0·011). There was a significant association of aneurysm diameter with the Ava II genotype. Patients homozygous for the common allele (1–1) had the lowest median aortic diameter and those homozygous for the rare allele (2–2) the highest, with heterozygotes (1–2) being intermediate (*Figure 1*). Possession of the rare allele (1–2 or 2–2) was associated with an increased aneurysm diameter (P = 0·044). There was no association of aneurysm diameter with the Ala → Thr (Alu I) polymorphism or haptoglobin phenotype. The presence of the rare Ava II allele was also associated significantly with an increased pressure–strain elastic modulus (stiffness) of the aneurysmal wall. In 14 patients of 1–1 genotype the median pressure–strain elastic modulus was 23·9 N/cm^2 compared with 42·0 N/cm^2 in 11 of 1–2 genotype (P = 0·008, Mann–Whitney U test) (*Figure 2*). Pressure–strain elastic modulus was not determined in any patient of 2–2 Ava II genotype.

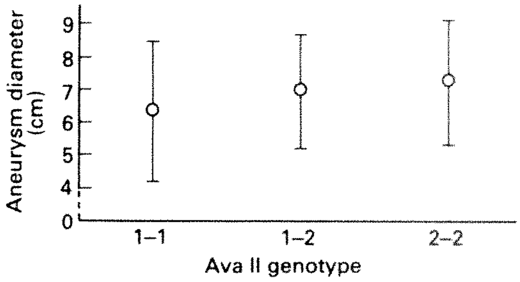

Figure 1 *Variation of aneurysm diameter with collagen III genotype. The mean(s.d.) diameter is given for each genotype determined by Ava II digestion. 1–1 Genotype,* n = *64; 1–2,* n = *50; 2–2,* n = *11. Presence of the rare (2) allele was associated with an increased aneurysm diameter* (P = *0·044, analysis of variance*)

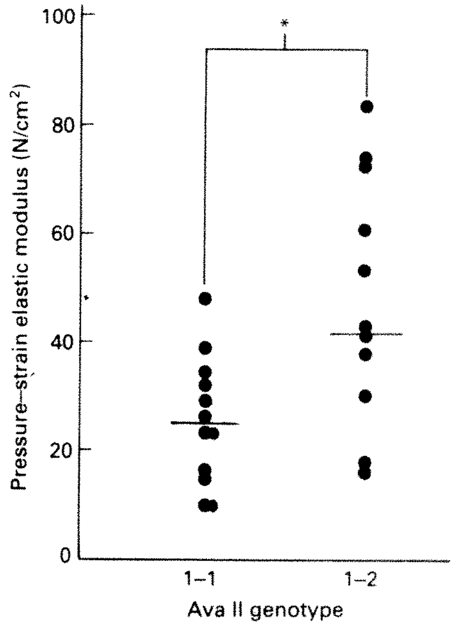

Figure 2 *Variation of pressure–strain elastic modulus with collagen III genotype. The median (interquartile range) value in patients of 1–1 Ava II genotype was 23·9 (16·5–32·6) N/cm^2 compared with 42·0 (30·5–73·0) N/cm^2 in those of 1–2 genotype.* *P = *0·008 (Mann–Whitney* U *test*)

Table 1 *Details of the three patient groups*

	Abdominal aortic aneurysm (n = 153)	Aortoiliac stenosis (n = 87)	Peripheral arterial disease (controls) (n = 98)
Age (years)*	68(7)†	66(8)	66(10)
Proportion of men (%)	82†	74	65
>20 pack-years smoking (%)	87	100	93
Diabetes (%)	3†	14	13
Ischaemic heart disease (%)	27	33	35
Mean blood pressure (mmHg)			
Systolic	151	149	148
Diastolic	88	85	86
Aortic diameter (mm)*	7·0(3·0)	1·8(0·4)	1·9(0·5)
Height (m)*	1·74(0·08)†	1·68(0·10)	1·69(0·10)
Cholesterol level (mmol/l)*	6·7(1·3)	7·0(1·9)	6·6(1·7)

*Values are mean(s.d.). †$P < 0·01$ (aneurysm *versus* stenosis and control groups)

Table 2 *Type III collagen genotypes*

	Abdominal aortic aneurysm		Aortoiliac stenosis		Peripheral arterial disease (controls)	
	No. of patients	Frequency of allele	No. of patients	Frequency of allele	No. of patients	Frequency of allele
Alu I (Thr-531)	144	0·253†	85	0·253†	98	0·352
Ava II (3′ flanking)	125	0·288	86	0·186‡	—	(0·27)*
619 Gly → Arg mutation	150	0	50	0	—	—

*Population frequency[10]; in 65 control patients in a cardiovascular health screening programme the frequency of the rare allele was 0·27. †$P < 0·05$ (aneurysm and stenosis groups *versus* controls); ‡$P < 0·05$ (stenosis *versus* aneurysm group) (χ^2 test)

Discussion

Patients with AAA are more likely to have an aneurysm elsewhere, for example in the femoral, popliteal or carotid arteries, indicating a general tendency for dilating aneurysmal disease. Other patients have stenosing lesions in the aorta, iliac and other distal arteries. Atherosclerosis is certainly the cause of these stenosing lesions but commonly is also present in aneurysmal disease. The elastic and other mechanical properties of the aorta and other arteries could influence whether, in the presence of ageing and atherosclerosis, an artery dilates or stenoses. Such mechanical properties may be under genetic control, since mutational change in components of arterial connective tissue is the cause of both arterial dilatation in Marfan's syndrome and the arterial fragility of Ehlers–Danlos type IV disease.

With ageing and disease, the elastin content of the aortic media decreases, thereby shifting the mechanical load of the pulse pressure from elastin on to collagen[9,12]. In this situation subtle variations in the structure or content of type III collagen could influence the mechanical properties of the aorta and hence its susceptibility to disease. The present results add weight to this hypothesis. For patients with AAA, polymorphic variation in the region 3′ to the type III collagen gene detected with the restriction enzyme Ava II was associated with both aneurysm diameter and pressure–strain elastic modulus. Although this polymorphism lies outside the type III collagen gene, it is detected using a collagen gene probe and so lies sufficiently close to the 3′ region of the gene to act as a marker for variation in this region. The presence of the rare Ava II allele was significantly less common in patients with aortoiliac stenosis than in those with AAA. These results are a clear indication of a genetic influence on disease in the ageing aorta. Such genetic influence may determine whether, in the presence of atherosclerotic risk factors, the aorta stenoses or dilates; it might also determine how rapidly an aneurysm grows.

In contrast, the results for the 531 Ala → Thr polymorphism and the 619 Gly → Arg mutation within type III collagen provide no support for the presence of a single common founder mutation in type III collagen predisposing to AAA. It is interesting that patients with distal arterial disease without a significant aortoiliac component have an increased frequency of Thr-531 in type III collagen. Again, this could indicate that subtle variation in collagen influences the mechanical properties of the ageing aorta and hence its susceptibility to disease.

In summary, an important contribution to the development of AAA may result from the influence of variation in the type III collagen gene on the mechanical stability of the ageing aorta. Whether possession of the rare Ava II allele of the type III collagen gene is associated with more rapid aneurysmal dilatation or rupture is being studied prospectively.

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Early detection of occult colorectal hepatic metastases using duplex colour Doppler sonography

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Previous studies have shown that overt intrahepatic tumours are associated with subtle changes in liver perfusion that can be measured directly using duplex colour Doppler sonography (DCDS). This study assessed the predictive value of DCDS in the early detection of occult colorectal hepatic metastases. Hepatic arterial and portal venous blood flow was measured in 50 control subjects and 135 patients with colorectal cancer, 67 with overt liver metastases and 68 with an apparently disease-free liver on the basis of computed tomography and laparotomy findings. The Doppler perfusion index (DPI), defined as the ratio of hepatic arterial to total liver bloodflow, was calculated. Clear separation of the DPI values of controls and those of patients with overt metastases was observed ($P < 0.0001$). Thirty-eight of the 68 patients with a disease-free liver also had an abnormally high DPI value. After 1 year of follow-up, 21 patients with an abnormally high DPI at the time of apparently curative primary resection had developed liver metastases and a further four had died without post-mortem examination. The 30 patients with normal DPI remain disease-free. The data suggest that DPI is of value in the early detection of occult liver metastases.

Colorectal cancer is the second most common malignancy in the UK, with 27000 new cases each year. About 25 per cent of patients have evidence of hepatic metastases at the time of presentation[1] and their prognosis is poor. Furthermore, for patients who have had an apparently curative resection of the primary tumour, the 5-year survival rate is only 50 per cent, with the majority dying from disseminated disease within the first 3 years. Finlay and McArdle[2] have shown that occult liver metastases are present in about 25 per cent of those who have undergone apparently curative resection. This finding has been supported by other workers[3] using intraoperative ultrasonography. The presence or absence of these liver metastases determines the likelihood of dying from disseminated disease.

The early detection of occult liver metastases is therefore important but appears to be beyond the resolution of current imaging techniques such as conventional ultrasonography, computed tomography (CT) and magnetic resonance imaging. There is a threshold size and contrast below which the differentiation between normal and abnormal tissue is impossible. Although recent advances in these cross-sectional imaging techniques have led to the detection of subcentimetre lesions, these are too small to have any characteristic morphological feature of diagnostic value and further follow-up with repeated radiological scanning is required.

There has been much interest in measurement of the subtle changes in hepatic perfusion associated with the presence of liver tumours. Previous studies using dynamic scintigraphy have shown that the presence of liver metastases can be diagnosed by measuring the ratio of hepatic arterial to total liver blood flow (the hepatic perfusion index) as described by Leveson and colleagues[4]. However, this technique has not gained support in clinical practice because of difficulties in the interpretation of data and lack of reproducibility[5]. Over the past 18 months a novel method has been developed to measure changes in liver perfusion using duplex colour Doppler sonography (DCDS). This is a more direct technique of non-invasive blood flow measurement, which should be more accurate. This study assessed the predictive value of DCDS in the early detection of occult colorectal hepatic metastases.

Patients and methods

Fifty healthy volunteers (age 23–75 years) and 135 patients with colorectal cancer (age 32–75 years) were studied. The technique for measuring hepatic arterial and portal venous blood flows has previously been described[6]. All subjects were examined in the supine position after 12 h of fasting. Using DCDS, the hepatic arterial and portal venous blood flows were calculated from the product of the measured time-average velocity of blood in the vessel and the time-average cross-sectional area of the lumen of the vessel. The total liver blood flow was taken as the sum of the hepatic arterial and portal venous blood flows. The Doppler perfusion index (DPI), defined as the ratio of the hepatic arterial to total liver blood flow, was calculated.

Anatomical variations were present in 20 of 67 patients (30 per cent) with liver metastases as confirmed by hepatic arteriography and in 16 of 68 (24 per cent) with an apparently 'clear' liver on the basis of DCDS only. Control subjects with anatomical variations were excluded from the study. The two main variations easily identified by DCDS in this study were: (1) both right and left hepatic arteries arising from the superior mesenteric artery; and (2) left hepatic artery arising from the coeliac axis and the right hepatic artery from the superior mesenteric artery. Sometimes an accessory right hepatic artery with its origin in the superior mesenteric artery could also be identified by the smaller calibre of the vessel. When hepatic arterial anatomical variation occurred, the total hepatic arterial blood flow was taken as the sum of the blood flows from the aberrant hepatic arteries.

Technique of Doppler flow measurement

A Diasonics Spectra scanner (Diasonics Sonotron, Bedford, UK), which contains duplex and colour Doppler facilities, was used with a 3·5-MHz convex phased linear-array probe. In the Doppler mode, ultrasound waves were emitted and received by a single 3·5-MHz probe at a frequency of 3 MHz with a repetition frequency of 3·7 kHz. It was possible to steer the Doppler beam to any location, and the angle between the beam and the vessel examined could be measured from the monitor. An angle range of 50–68° was used for velocity measurement. Spectral analysis was performed using fast Fourier

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transformation and the Doppler shift signal was displayed on the monitor. The system was equipped with software to compute the time-average velocity from the velocity spectral display automatically, following placement of the calipers at the start and end of one or more cardiac cycles. The cross-sectional area of the vessel was measured by mapping the perimeter of the vessel lumen with a 'tracker ball'.

A transverse scan was made at the epigastrium to locate the common hepatic artery in its longitudinal axis. The Doppler cursor was placed over the lumen of the artery segment as near to the origin as possible, at the point where it first became horizontally straight. The Doppler sample volume and beam angle were adjusted and the time-average velocity calculated over four cardiac cycles. The cross-sectional area of the artery was measured at the same point at right angles to the vessel. Time-average cross-sectional area was calculated by taking the mean of the areas measured separately over four different cardiac cycles. The same parameters were obtained for the portal vein in a similar manner at the mid-level of the vein. All measurements were performed under respiratory suspension in expiration to allow optimal visualization of the portal vein and enable a more acute angle to be achieved for Doppler purposes. Each measurement was performed repeatedly until satisfactory spectral patterns were obtained. These measurements were carried out by an independent ultrasonographer with no knowledge of the preoperative CT and ultrasonography findings. No sonographic assessment of the liver parenchyma was made while performing the DPI measurement.

Conventional non-enhanced and enhanced dynamic CT was performed in all patients with colorectal cancer before operation using a GE 9800 CT scanner (Milwaukee, Wisconsin, USA). Enhanced scans were performed using a peripheral intravenous bolus injection (150 ml) of Ultravist 370 (iopromide; Schering Health Care, Burgess Hill, UK) administered by an Angiomat CT injector (Liebel-Flarsheim, Cincinnati, Ohio, USA).

Patients with an apparently disease-free liver on the basis of laparotomy and CT findings were subsequently followed by routine outpatient clinical examination, ultrasonography at intervals of 3 months, and annual CT (earlier if clinically indicated).

Informed consent was obtained from all subjects. Data were analysed using the Mann–Whitney *U* test.

Results

On the basis of CT and laparotomy findings, 67 patients had liver metastases and 68 an apparently curative resection. There was a significant increase ($P < 0{\cdot}0001$) in the time-average velocity and cross-sectional area of the hepatic artery in patients with liver metastases compared with controls. Hepatic arterial blood flow was therefore significantly higher ($P < 0{\cdot}0001$) in the group with metastases (*Table 1*). However, there was a significant reduction in the time-average velocity ($P < 0{\cdot}001$) and cross-sectional area ($P < 0{\cdot}0001$) of the portal vein in patients with hepatic metastases compared with the control group. The portal venous blood flow was significantly lower ($P < 0{\cdot}0001$) in patients with liver metastases than in controls (*Table 1*). No significant difference was demonstrated between these two groups in the total liver blood flow.

The upper limit of the normal range of DPI values was 0·25; the range for patients with hepatic metastases was 0·30–0·77. Clear separation of the DPI values was observed between controls and patients with overt liver metastases ($P < 0{\cdot}0001$) (*Figure 1*). The results for the 68 patients in the third group (those with an apparently disease-free liver) overlapped those of controls and patients with overt liver metastases. Thirty-eight of the 68 patients had an abnormally raised DPI. At the 1-year follow-up, 21 of these 38 patients had developed liver metastases, of whom nine had died. Two further patients had died with local recurrence of the primary tumour but hepatic metastases could not be excluded at the time of death. Another two patients died at home and no autopsy was carried out. Thirteen patients with an abnormal DPI have not yet shown evidence of dissemination and require further follow-up. The remaining 30 patients with a normal DPI are still alive and remain disease-free on the basis of clinical evidence, ultrasonography and CT. At 1 year of follow-up, excluding the four patients whose liver status was unknown, the sensitivity, specificity, and positive and negative predictive values of the test in the third group were 100, 70, 62 and 100 per cent respectively.

Of the 30 patients who had an apparently curative resection of the primary tumour with a normal DPI value, ten had Dukes' C, 19 Dukes' B and one Dukes' A disease. Of the 38 patients with an abnormal DPI value, 22 had Dukes' C and 16 Dukes' B tumours. Of the 21 patients who subsequently developed overt liver metastases within 1 year of follow-up, 18 had Dukes' C and three Dukes' B disease; vascular invasion by the primary tumour was present in six patients.

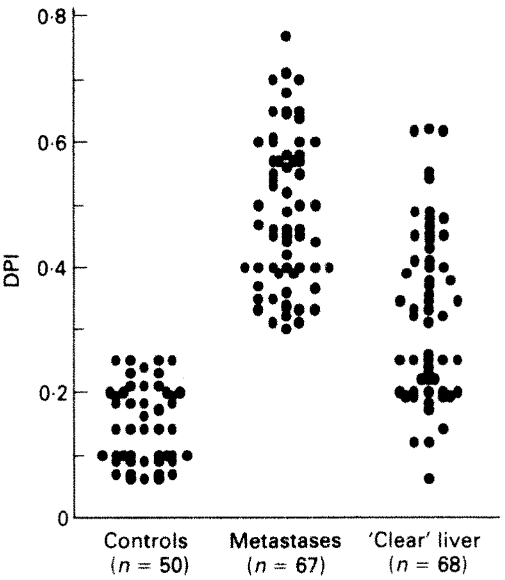

Figure 1 *Doppler perfusion index (DPI) values in 50 control subjects, 67 patients with overt liver metastases and 68 with an apparently metastasis-free liver*

Table 1 *Summary of results*

	Controls (*n* = 50)	Liver metastases (*n* = 67)	'Clear' liver (*n* = 68)
Hepatic artery			
Cross-sectional area (mm²)	17·0(5·0)	32·0(14·5)†	20·6(7·0)
Time-average velocity of blood (cm/s)	19·0(10·0)	33·0(12·0)†	27·5(11·0)
Blood flow (ml/min)	194(125)	630(330)†	336(177)
Portal vein			
Cross-sectional area (mm²)	129·0(36·0)	99·0(26·6)†	97·0(25·0)
Time-average velocity of blood (cm/s)	15·0(6·0)	11·2(4·0)*	12·3(3·3)
Blood flow (ml/min)	1200(570)	670(340)†	720(260)
Total liver blood flow (ml/min)	1390(640)	1300(580)	1043(315)
Doppler perfusion index	0·14(0·06)	0·49(0·13)†	0·32(0·12)

Values are mean(s.d.). *$P < 0{\cdot}001$; †$P < 0{\cdot}0001$ (liver metastases *versus* controls, Mann–Whitney *U* test)

Discussion

The clinical value of qualitative data provided by duplex ultrasonography is widely recognized but there is still some discussion about the value of quantitative measurements. While the accuracy and reproducibility of flow measurements have been well documented *in vitro* and *in vivo* at research level, there is still some scepticism regarding its application in clinical practice. The wide variety of commercially available duplex scanners that have not been properly calibrated has led to inconsistency of quantitative data. Kimme-Smith and colleagues[7] have compared measurements of peak velocities obtained using 17 different scanners with values obtained from calibrated phantoms. The mean variation among the various systems was 23 per cent under identical conditions. Some units gave peak velocities that were > 100 per cent too high compared with calibrated peak velocities. The authors advised that quantitative measurements obtained using Doppler ultrasonography should be reported, with information on the calibration of the equipment.

The authors have previously demonstrated[8,9] the accuracy of duplex colour Doppler flowmetry *in vitro* and the reproducibility of the hepatic arterial and portal venous blood flow measurements *in vivo*. Following repeated measurements of the flow parameters in each vessel for five healthy volunteers, the mean coefficients of variation for time-average velocity, cross-sectional area and blood flow were 4·5, 6·1 and 7·6 per cent respectively. The potential sources of error involved are: (1) non-uniform insonation of the vessel; (2) spectral broadening; (3) angle correction; (4) area estimation; and (5) errors in the processing facilities of the system. However, some of these can be minimized by standardizing the technique used to make each measurement. Addition of a colour Doppler facility to the conventional duplex scanner is of great advantage in the precise assessment of vessel geometry and accurate identification of vessels of interest; it shows anatomical variations and allows a significant reduction in the duration of scanning. The technique is, however, operator dependent and a dedicated ultrasonographer is essential.

The arterial blood supply to the liver is quite variable. Although account was taken in the present study of anatomical variations when detected, underestimation of hepatic arterial blood flow would have occurred when the left hepatic artery and/or an accessory left hepatic artery arose from the left gastric artery, as they would not have been identified by DCDS. If that were the case in patients with an abnormal DPI, the true DPI value would be even higher and would, therefore, have remained abnormal. Underestimation of hepatic arterial flow could in theory lead to false-negative results, but no patient with a normal DPI has yet developed liver metastases.

Despite the potential sources of error involved in the technique, clear separation of the DPI values of all patients with overt liver metastases was observed compared with controls. This suggests that DCDS measurement of DPI can reliably detect patients with colorectal cancer and overt hepatic metastases. The upper limit of the normal range for the DPI is lower than the corresponding value for the hepatic perfusion index[4], which in theory measures the same blood flow ratio by dynamic scintigraphy. This presumably reflects the difference in technique; both may be subject to different types of systematic error. For example, the hepatic perfusion index may overestimate the true blood flow ratio because of dispersion of the tracer bolus in the splanchnic vascular bed.

The results of the third group of 68 patients who underwent apparently curative resection of the primary tumour are particularly interesting. Thirty-eight of these patients had abnormally high DPI values before laparotomy, and after 1 year of follow-up 21 had developed liver metastases, of whom nine had died. Furthermore, liver metastases may have been present in the other four patients who died. These initial data confirm the ability of DCDS measurement of DPI to detect occult liver metastases at the time when the patient first presents with colorectal cancer. Furthermore, the 30 patients who had normal DPI values showed no evidence of liver metastases after 1 year of follow-up, resulting in a negative predictive value of 100 per cent. Further follow-up to assess the long-term predictive value of the DPI is required. However, the implication is potentially far-reaching, especially at a time when the role of adjuvant therapy is still uncertain in the UK. About 50 per cent of patients undergoing curative resection do not require adjuvant therapy. Therefore, if patients at high or low risk could be identified reliably, adjuvant therapy could be administered on a selective basis. It has been suggested that adjuvant therapy should be regarded as standard practice in patients with Dukes' C carcinoma. If so, about 75 000 patients in Western Europe (including 8100 in the UK) and 45 000 in the USA could be expected to receive adjuvant therapy each year. Most regimens of systemic adjuvant chemotherapy are associated with varying degrees of toxicity and about 30 per cent of these patients would be expected to discontinue treatment prematurely because of toxicity[10]. The identification of the patients at low risk would prevent inappropriate treatment and avoid unnecessary morbidity.

In conclusion, the data suggest that measurement of the DPI by DCDS can reliably detect overt liver metastases and identify patients with occult liver metastases that will become clinically or radiologically apparent in the first year after operation.

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Ventilatory and blood gas changes during laparoscopic and open cholecystectomy

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As part of a randomized trial, ventilatory and arterial blood gas changes were assessed during open (n = *30*) *and laparoscopic* (n = *30*) *cholecystectomy. Measurements were made during anaesthesia before the start of surgery and at the time of removal of the gallbladder. Despite an increase in minute ventilation from a mean(s.d.) of 5·7(1·4) to 6·1(1·2) litres, mean(s.d.) arterial carbon dioxide tension* (P_{aCO_2}) *rose from 5·3(0·9) to 6·0(0·9) kPa during laparoscopic cholecystectomy. End-tidal carbon dioxide tension* ($P_{E'CO_2}$) *had poor precision in predicting* P_{aCO_2} *(95 per cent interval of agreement −0·61 to 1·93 kPa). Mean(s.d.) peak airway pressure increased from 17(4) to 23(4) cmH*$_2$*O. The mean* $P_{aCO_2} - P_{E'CO_2}$ *value did not change significantly, although there was significant within-patient variation. Arterial oxygen levels did not change significantly. By comparison, no clinically significant changes in ventilation or blood gas values occurred during open cholecystectomy. In conclusion, laparoscopic cholecystectomy requires a substantial but variable increase in minute ventilation to compensate for carbon dioxide absorption from the peritoneum.*

Until the advent of extended therapeutic procedures such as laparoscopic cholecystectomy, most laparoscopies were brief and were performed in young, fit patients. Ventilatory changes in these patients have been extensively studied and found to be clinically unimportant[1–4]. With the increasing popularity of minimally invasive general surgery, many laparoscopic procedures now require long periods of peritoneal insufflation and are often performed on patients who are older and have respiratory disease. Two recent studies[5,6] have suggested that in these circumstances greater ventilatory changes occur.

End-tidal carbon dioxide partial pressure ($P_{E'CO_2}$) monitoring is increasingly used during anaesthesia as an indirect measure of arterial carbon dioxide tension (P_{aCO_2}); the relationship between these two variables is therefore of considerable interest. The arterial–end-tidal P_{CO_2} difference, $P_{aCO_2} - P_{E'CO_2}$, depends on many factors including the relative distribution of ventilation and perfusion within the lung, and the functional residual capacity[7]. During laparoscopic procedures, changes in ventilation and perfusion distribution caused by basal lung compression might be expected to occur because of the pneumoperitoneum. Thus, $P_{aCO_2} - P_{E'CO_2}$ might be expected to change.

The present study assessed ventilatory and arterial blood gas changes during laparoscopic cholecystectomy (using open cholecystectomy as a control group), and assessed the accuracy of capnography in monitoring arterial carbon dioxide tension changes.

Patients and methods

This study was approved by the local hospital ethics committees. Informed consent was obtained from all patients, who were participating in a randomized trial comparing laparoscopic cholecystectomy and open cholecystectomy through a small subcostal incision. All patients undergoing elective cholecystectomy were considered for entry to the trial. Patients requiring emergency surgery, those with suspected bile duct stones and those with extensive previous upper abdominal surgery were excluded. Patients were randomized using numbered sealed envelopes. Thirty consecutive patients in each arm of the randomized trial were studied. Three patients in the laparoscopic group who required early conversion to open cholecystectomy were excluded.

Patients underwent general anaesthesia and were paralysed and ventilated. Anaesthetic techniques were similar in both groups; agents used were thiopentone or propofol for induction, suxamethonium for initial muscle relaxation, morphine and enflurane for maintenance, and atracurium besylate or vecuronium for muscle relaxation. An Ohmeda OAV 7750 ventilator (Ohmeda, Hatfield, UK) with a non-rebreathing circuit was used. Minute ventilation was recorded by a flow transducer on the expiratory side of the circuit. Peak airway pressure was recorded by an anaeroid pressure gauge in the ventilator. End-tidal carbon dioxide tension was measured throughout the operation using an infra-red analyser (Datex Capnomac Ultima; Instrumentation Corporation, Helsinki, Finland). The coefficient of variation for $P_{E'CO_2}$ measurement of values within the normal range is 0·2 per cent. Minute ventilation was adjusted to obtain $P_{E'CO_2}$ within the range 4·0–6·0 kPa. When $P_{E'CO_2}$ was stable, and just before the start of surgery, baseline recordings were made of minute ventilation, peak airway pressure, $P_{E'CO_2}$ and inspired oxygen fraction (F_{IO_2}). At the same time, an arterial blood sample was taken and analysed for oxygen tension (P_{aO_2}), carbon dioxide tension (P_{aCO_2}), and concentrations of hydrogen ion ([H$^+$]) and bicarbonate ([HCO$_3^-$]). The coefficient of variation for P_{aCO_2} measurements of values within the normal range is 1·4 per cent.

In patients undergoing laparoscopic cholecystectomy, pneumoperitoneum was achieved with carbon dioxide insufflation through a Veress needle to a maximum pressure of 15 mmHg. No patient developed surgical emphysema caused by a misplaced Veress needle. The operation was performed with the patient either horizontal or with a slight head-up tilt. During surgery, ventilation settings in both groups were adjusted according to changes in $P_{E'CO_2}$ (arterial blood gas results were not available to the anaesthetist). At the time of removal of the gallbladder, all measurements including arterial blood gas sampling were repeated.

Statistical analysis

Comparison between groups was made using Student's unpaired *t* test and within groups using the paired *t* test. The 95 per cent confidence intervals (c.i.) of the range of $P_{aCO_2} - P_{E'CO_2}$ values were calculated to assess the accuracy of capnography in monitoring P_{aCO_2} changes[8]. Correlations were tested with Pearson linear regression analysis.

Results

The groups were well matched for preoperative patient characteristics (*Table 1*). Results are summarized in *Tables 2* and *3*.

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Table 1 *Preoperative characteristics and pulmonary function*

	Cholecystectomy	
	Open ($n = 30$)	Laparoscopic ($n = 30$)
Mean (range) age (years)	51 (19–82)	54 (31–80)
Sex ratio (M:F)	5:1	6·5:1
Height (cm)*	160(8)	161(6)
Weight (kg)*	65(10)	69(11)
FVC (litres)*	2·87(0·64)	2·94(0·84)
FEV_1 (litres)*	2·32(0·61)	2·39(0·77)
PEFR (ml/s)*	370(112)	369(128)
Asthma	3	4
Chronic bronchitis	1	1

*Values are mean(s.d.). FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; PEFR, peak expiratory flow rate

Table 2 *Ventilation and blood gas measurements*

	Cholecystectomy			
	Open ($n = 30$)	Laparoscopic ($n = 30$)	t	P
Beginning of surgery				
Minute ventilation (litres)	5·4(1·2)	5·7(1·4)	0·8	0·44
$P_{E'CO_2}$ (kPa)	4·6(0·5)	4·6(0·6)	0·2	0·81
P_{aCO_2} (kPa)	5·2(0·7)	5·3(0·9)	0·6	0·57
Arterial $[H^+]$ (nmol/l)	40(4)	41(6)	0·9	0·38
$P_{aCO_2} - P_{E'CO_2}$ (kPa)	0·6(0·6)	0·7(0·7)	0·9	0·38
P_{aO_2} (kPa)	22·7(7·6)	19·1(7·1)	1·9	0·06
F_{iO_2} (%)	38(10)	38(7)	0·0	0·98
Peak airway pressure (cmH_2O)	17(4)	17(4)	0·3	0·79
$[HCO_3^-]$ (mmol/l)	25(2)	25(2)	0·2	0·86
At removal of gallbladder				
Minute ventilation (litres)	5·1(1·1)	6·1(1·2)	3·4	<0·001
$P_{E'CO_2}$ (kPa)	4·8(0·4)	5·4(0·7)	3·9	<0·001
P_{aCO_2} (kPa)	5·5(0·7)	6·0(0·9)	2·0	0·046
Arterial $[H^+]$ (nmol/l)	42(5)	46(5)	2·9	0·006
$P_{aCO_2} - P_{E'CO_2}$ (kPa)	0·8(0·5)	0·6(0·5)	0·0	0·36
P_{aO_2} (kPa)	19·6(4·7)	19·1(5·7)	0·3	0·76
F_{iO_2} (%)	37(7)	39(6)	−0·9	0·37
Peak airway pressure (cmH_2O)	18(4)	23(4)	5·3	<0·001
$[HCO_3^-]$ (mmol/l)	24(2)	24(2)	0·4	0·64

Values are mean(s.d.). Abbreviations are defined in the text

Table 3 *Statistical comparison within patients of ventilatory and blood gas changes*

	Cholecystectomy			
	Open		Laparoscopic	
	t	P	t	P
Minute ventilation	1·4	0·16	2·0	0·049
$P_{E'CO_2}$	1·0	0·31	6·5	<0·001
P_{aCO_2}	2·4	0·021	4·5	<0·001
Arterial $[H^+]$	3·3	0·002	6·5	<0·001
$P_{aCO_2} - P_{E'CO_2}$	1·8	0·069	0·9	0·35
P_{aO_2}	1·7	0·10	0·7	0·51
F_{iO_2}	1·2	0·22	0·4	0·68
Peak airway pressure	2·3	0·025	11·4	<0·001

Baseline readings are compared with those at gallbladder removal. Abbreviations are defined in the text

Baseline results

On baseline measurements, the two groups were well matched for ventilatory and blood gas values. $P_{E'CO_2}$ was of low accuracy in predicting P_{aCO_2}: the 95 per cent interval of agreement was −0·61 to 1·93 kPa.

Measurements at time of gallbladder removal

The mean (range) time between beginning surgery and the second set of measurements was 40 (20–95) min in patients undergoing open cholecystectomy, compared with 61 (30–115) min in those having the laparoscopic procedure ($t = 4·1$, $P < 0·001$). All patients remained haemodynamically stable throughout surgery.

In the open cholecystectomy group, no clinically significant changes occurred in ventilatory or arterial blood gas values (*Table 2*).

For laparoscopic cholecystectomy, induction of a carbon dioxide pneumoperitoneum resulted in a progressive rise in $P_{E'CO_2}$ in the majority of patients. Despite a significant increase in minute ventilation, P_{aCO_2} and arterial $[H^+]$ both increased significantly. There was no correlation between the duration of pneumoperitoneum and the rise in either minute ventilation ($r = 0·27$, $P = 0·15$) or P_{aCO_2} ($r = 0·25$, $P = 0·18$). Pneumoperitoneum was also associated with a mean rise of 6 cmH_2O in peak airway pressure. There were no significant changes in $P_{aCO_2} - P_{E'CO_2}$, P_{aO_2} or F_{iO_2}.

As in baseline measurements, at the time of gallbladder removal $P_{E'CO_2}$ was of low accuracy in predicting P_{aCO_2} (95 per cent interval of agreement −0·4 to 1·6 kPa in both groups). Furthermore, there was poor concordance between $P_{aCO_2} - P_{E'CO_2}$ at the two time points (95 per cent interval of agreement between the baseline and second measurement for open cholecystectomy was −0·8 to 1·21 kPa and for the laparoscopic procedure −1·5 to 1·3 kPa).

Discussion

There have been numerous studies of ventilatory changes during laparoscopic gynaecological procedures with carbon dioxide pneumoperitoneum. Carbon dioxide absorption during laparoscopy performed under local anaesthesia results in an increased respiratory drive, with minute ventilation increasing by a mean of 1 l/min to maintain P_{aCO_2} within the normal range[9]. On the other hand, during laparoscopy under relaxant general anaesthesia with fixed minute ventilation volume, mean P_{aCO_2} is reported[1,4,10–12] to rise by 0·6–1·4 kPa.

There are only two published studies of blood gas changes during laparoscopic cholecystectomy[5,6]. Wittgen *et al.*[5] compared changes in 20 normal patients with those in ten with cardiorespiratory disease. During laparoscopic cholecystectomy, P_{aCO_2} rose by 0·8 kPa in the normal patients (without increasing ventilation), whereas in those with cardiopulmonary disease P_{aCO_2} rose by 2·0 kPa despite an increase in minute ventilation of 1·2 litres. The corresponding alterations in $P_{E'CO_2}$ were much lower and did not fully reflect the changes in P_{aCO_2}: in normal patients $P_{E'CO_2}$ increased by only 0·3 kPa, while in those with cardiorespiratory disease it rose by only 0·6 kPa. In contrast, in the present study and in an analysis of gynaecological laparoscopy[10], mean $P_{aCO_2} - P_{E'CO_2}$ did not change significantly with carbon dioxide pneumoperitoneum. Nevertheless, the present finding of poor concordance between the baseline value of $P_{aCO_2} - P_{E'CO_2}$ and the value at the end of the procedure supports the conclusion of Wittgen *et al.*[5] that end-tidal measurement of P_{CO_2} is a poor indicator of changes in P_{aCO_2}. Marked within-patient variability in $P_{aCO_2} - P_{E'CO_2}$ during anaesthesia has also been shown in a study of patients undergoing major surgery[13]. Indeed, within-patient variations in $P_{aCO_2} - P_{E'CO_2}$ were similar to or greater than inter-patient differences.

In the only other study of blood gas and ventilatory changes during laparoscopic cholecystectomy, Liu *et al.*[6] found that $P_{E'CO_2}$ and P_{aCO_2} both increased by a mean of 1·4 kPa during laparoscopic cholecystectomy, with 13 of 16 patients requiring an increase in minute ventilation to maintain $P_{E'CO_2}$ below 6 kPa. They claimed that there was good agreement between paired $P_{E'CO_2}$ and P_{aCO_2} measurements, but their data do not support this statement. On analysing their results, we calculate that the 95 per cent interval of agreement between P_{aCO_2} and $P_{E'CO_2}$ was $-0{\cdot}42$ to 1·08 kPa.

In a pig model of laparoscopic cholecystectomy, P_{aCO_2} increased by 1·9 kPa and carbon dioxide output by 30 per cent of baseline values[14]. In a canine model of prolonged laparoscopy (2 h), the effects of carbon dioxide and helium pneumoperitoneum were compared[15]. Even with a 57 per cent increase in minute ventilation to maintain constant $P_{E'CO_2}$, carbon dioxide pneumoperitoneum was associated with a significant rise in P_{aCO_2} and $P_{aCO_2} - P_{E'CO_2}$. The rise in minute ventilation requirement, P_{aCO_2} and $P_{aCO_2} - P_{E'CO_2}$ was greater in dogs with papain-induced pulmonary emphysema, supporting the findings of Wittgen *et al.*[5] in patients with pulmonary disease undergoing laparoscopic cholecystectomy. Intraoperative blood gas monitoring may be advisable in patients with severe respiratory disease[5], as they may have larger differences between P_{aCO_2} and $P_{E'CO_2}$ and a greater tendency to retain carbon dioxide.

Helium has recently been suggested as an alternative insufflation gas to carbon dioxide in patients with severe respiratory disease[15,16]. It is inert, non-combustible and cheap; its only drawback is that it is relatively insoluble. To reduce the risk of insoluble gas vascular embolism with helium pneumoperitoneum, the open technique of laparoscopy might be used[17], which avoids the risk of insufflation through a misplaced Veress needle. Alternatively, the initial pneumoperitoneum could be created using carbon dioxide and, once pneumoperitoneum is safely established, carbon dioxide could be replaced by helium as the maintenance gas.

During laparoscopic procedures, changes in ventilation and perfusion distribution might be expected to occur because of the raised intra-abdominal pressure. However, in this study $P_{aCO_2} - P_{E'CO_2}$ and P_{aO_2} during pneumoperitoneum were not significantly different from values observed before insufflation or those in patients undergoing open surgery.

In conclusion, laparoscopic cholecystectomy with carbon dioxide pneumoperitoneum is associated with a significant increase in carbon dioxide output, requiring a significant but variable increase in minute ventilation to prevent hypercarbia. $P_{E'CO_2}$ is of low accuracy in predicting P_{aCO_2}. We therefore suggest that ventilation be increased to maintain $P_{E'CO_2}$ towards the lower end of the normal range (4–5 kPa).

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Comparison of metabolic responses to laparoscopic and minilaparotomy cholecystectomy

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This randomized study compared the metabolic responses to laparoscopic cholecystectomy ($n = 10$) *and minilaparotomy cholecystectomy with a 5–7-cm incision* ($n = 10$)*. Venous blood samples were taken before operation and at 3, 6, 9, 12, 18, 24, 48, 72 and 168 h after incision and analysed for levels of C-reactive protein, interleukin 6, cortisol, albumin, transferrin, iron, fibrinogen, fibrin degradation products and polymorphonuclear elastase, and for neutrophil and lymphocyte counts. Urine samples (24 h) were analysed for urea, creatinine, 3-methylhistidine and catecholamines. The magnitude of the metabolic changes from baseline levels was quantified by calculating areas under each individual curve. A significant metabolic response with a similar time course and magnitude of changes occurred after laparoscopic and minilaparotomy cholecystectomy but with wide variation in magnitude between individuals.*

The stress of surgery leads to production of cytokines and acute-phase proteins, increases in the levels of 'stress' hormones, loss of muscle protein, greater vascular permeability and changes in white cell count subsets. Some of these responses are a homoeostatic defence mechanism, but others such as the catabolic state are thought to be deleterious[1]. Many investigators[2–6] have therefore tried to find ways of reducing the metabolic response to surgery.

The use of a small transverse incision for open cholecystectomy (minilaparotomy) has been shown to result in a more rapid postoperative recovery than a standard laparotomy[7–13]. Laparoscopic cholecystectomy is replacing the open operation as the procedure of choice for symptomatic cholelithiasis[14]. The advantages claimed are less postoperative pain[15] and a more rapid return to normal activity[14].

The magnitude of the metabolic response to surgical trauma is proportional to the degree of injury[16–19], and the reduction of 'access trauma' by laparoscopic techniques might therefore diminish the response[20]. Diagnostic laparoscopy alone is associated with a substantial hormonal and glycaemic response, which may be evoked by the stimulus of peritoneal distension[21]. The magnitude of the metabolic response correlates with the duration of surgery[17,22], which is longer for laparoscopic than open cholecystectomy[23].

This study compared the pattern and magnitude of the metabolic response to injury after laparoscopic and minilaparotomy cholecystectomy as part of a randomized trial evaluating the two procedures[24,25].

Patients and methods

The trial was approved by the local hospital ethical committees and informed consent obtained from all patients. Those with suspected common bile duct stones were excluded. Detailed metabolic studies were performed in ten consecutive patients in each arm of the trial. Patients requiring conversion to open cholecystectomy, those with medical conditions or receiving treatment that might result in an altered metabolic response to surgery and patients who developed complications were excluded. The median (range) age of patients undergoing laparoscopic cholecystectomy was 58 (30–71) years and in the minilaparotomy group 44 (25–70) years. There was one man in each group.

Anaesthetic techniques were similar in the two groups. Minilaparotomy cholecystectomy was performed through a 5–7-cm subcostal incision[11]. Laparoscopic cholecystectomy was performed by a four-cannula technique using electrocautery. Wounds in both groups were infiltrated with 20 ml 0·5 per cent bupivacaine at the end of the procedure. The median operating time was longer for laparoscopic cholecystectomy (65 *versus* 46 min, $P = 0{\cdot}01$). After operation, patients received morphine by a disposable patient-controlled analgesia device[26] (PCA infusor system; Baxter Healthcare, Thetford, UK). For the first 24 h after operation, patients were given intravenous fluids (1 litre normal saline, 2 litres 5 per cent dextrose), and thereafter allowed free fluids and a normal diet. All patients made an uneventful postoperative recovery.

Blood was collected from an indwelling venous cannula on the morning of surgery (before premedication), and at 3, 6, 9, 12, 18, 24, 48, 72 and 168 h after incision. Urine samples (24 h) were collected the day before surgery, and over the first, second, third and seventh days after operation.

The level of the cytokine interleukin (IL) 6, which is thought to play a central role in the development of the metabolic response[27], was measured by the hybridoma growth stimulation assay using the mouse B cell hybridoma 7TD1 line[17,22,28]. Cell numbers were evaluated colorimetrically using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (thiazolyl blue)[29]. Standardization[30] was performed using recombinant IL-6 (National Institute of Biomedical Standards and Controls, Potters Bar, UK). Serum samples were heat-treated to inactivate any inhibitors. The detection limit was 14 units/ml and the coefficient of variation 19 per cent.

Levels of the positive acute-phase proteins, C-reactive protein (CRP) and fibrinogen, and of the negative acute-phase proteins, albumin and transferrin (falls in which reflect increased vascular permeability and loss to the tissue spaces[31]), were measured by nephelometry. The detection limit for serum CRP was 5 mg/l. Serum iron, levels of which fall after surgery[32], was measured colorimetrically using a Hitachi 737 analyser (Boehringer Mannheim, Mannheim, Germany).

Neutrophil and lymphocyte counts were determined with a Coulter Blood Analyser (Coulter, Basingstoke, UK). Levels of plasma cross-linked fibrin degradation products (FDPs), a measure of fibrin turnover, were determined using an enzyme-linked immunosorbent assay (AGEN; Parsippany, New Jersey, USA). The cortisol concentration was measured by fluorescence polarization immunoassay. Levels of polymorphonuclear elastase, which is released by activated neutrophils[33], were measured using the polymorphonuclear elastase IMAC immunoactivation kit (Diagnostica Merk, Frankfurt, Germany).

Urinary 3-methylhistidine concentration, an indicator of muscle protein breakdown[34], was measured by ion-exchange chromatography with ninhydrin detection. Urinary creatinine levels were determined using the alkaline picrate reaction and urea measured electrochemically using a Beckman CX-3 instrument (Beckman, High Wycombe, UK). Urinary nitrogen was calculated on the basis that urea loss comprises 80 per cent of total nitrogen loss.

Because of different collection conditions, urine for catecholamine measurement had to be collected from a second group of 20 patients, ten in each arm of the study, with median (range) ages 56 (27–72)

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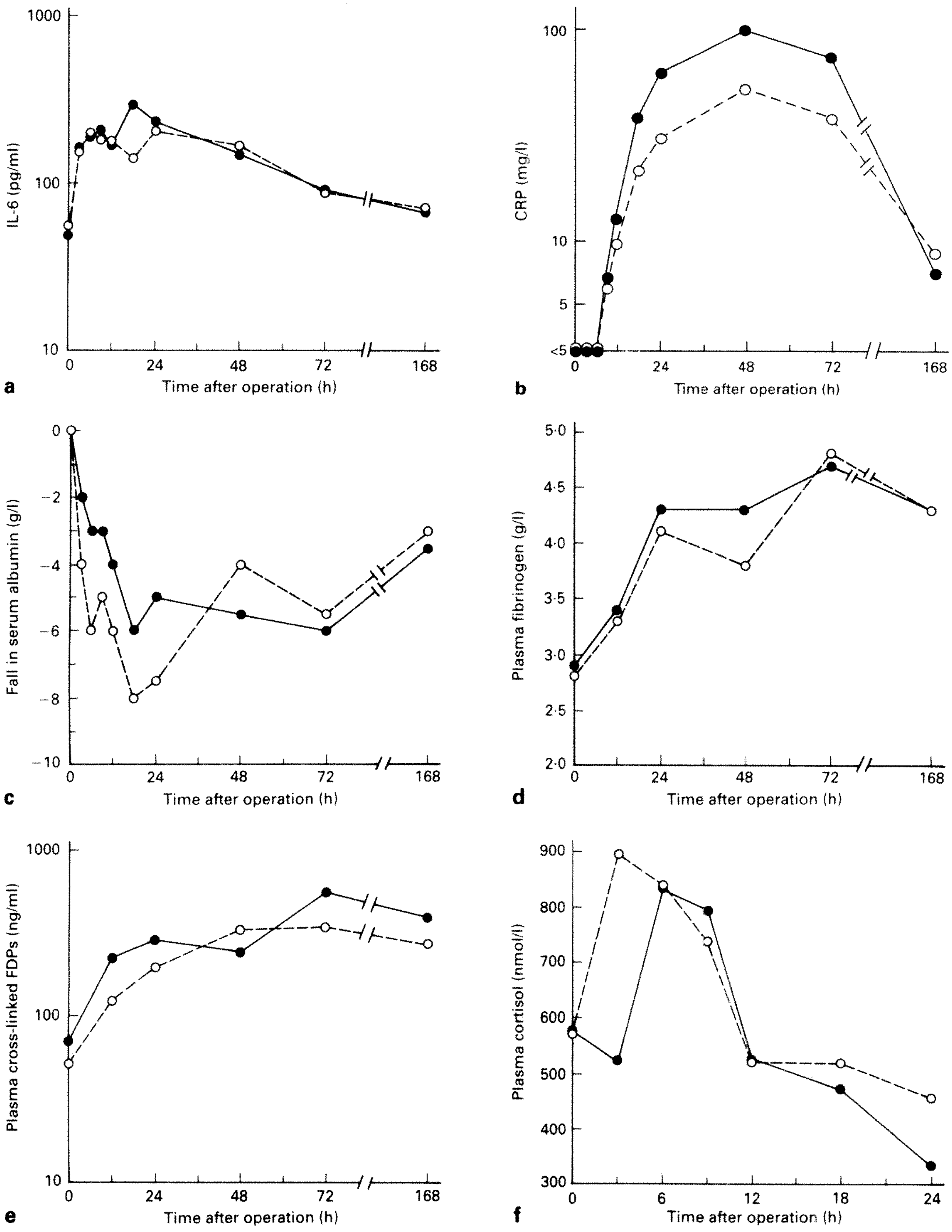

Figure 1 *Changes in* **a** *serum interleukin (IL) 6,* **b** *serum C-reactive protein (CRP),* **c** *serum albumin,* **d** *plasma fibrinogen,* **e** *plasma cross-linked fibrin degradation products (FDPs) and* **f** *plasma cortisol after laparoscopic* (○) *and minilaparotomy* (●) *cholecystectomy. Values are medians. There were no significant differences between the two groups in any of the parameters measured*

years in the laparoscopic group and 45 (19–82) years in the minilaparotomy group. (There were no men undergoing laparoscopic cholecystectomy and two having the minilaparotomy operation.) Urinary catecholamine levels were measured using high-performance liquid chromatography with electrochemical detection[35].

Peak expiratory flow rate was measured the day before and 24 h after operation with a Respiradyne pulmonary function monitor (Sherwood Medical, Crawley, UK). Analgesia consumption over the first 24 h was evaluated using patient-controlled delivery of morphine and pain assessed by a linear analogue score at 24 h.

Statistical analysis

To produce summary measures[36], each parameter was plotted against time and the area under the curve calculated individually for each patient using a program on a personal computer. For the two negative acute-phase reactants, albumin and transferrin, falls from preoperative values were plotted. Areas under the curves in the two groups were compared using the Mann–Whitney *U* test. The magnitude of changes in each metabolic variable (areas under the curve) were compared by the Pearson correlation coefficient (r). Values of white cell counts, urinary nitrogen, 3-methylhistidine and catecholamines in the two groups were compared at each time point using the Mann–Whitney *U* test with the Bonferroni correction as appropriate. Comparison of postoperative and preoperative catecholamine and 3-methylhistidine levels was performed with the Wilcoxon matched pairs test with the Bonferroni correction.

Results

The time courses of some of the metabolic changes measured are shown in *Figure 1*. Similar time courses of metabolic changes occurred in the two groups.

The calculated areas under the curves for the various parameters measured are shown in *Table 1*. There were no significant differences in the magnitude of the changes between the two groups. Patients undergoing laparoscopy, however, had better postoperative pulmonary function, consumed less morphine and had lower pain scores than those receiving minilaparotomy (*Table 2*).

There were no significant differences in urinary nitrogen loss (data not given). Food intake was not measured, therefore nitrogen balance could not be calculated, but both groups started eating on the first day. After operation, urinary 3-methylhistidine levels did not differ significantly from preoperative values and were all within the normal range (data not given).

There were no significant intergroup differences in catecholamine levels at the three time points with or without the Bonferroni correction (data not given).

There were significant associations between the response areas of several metabolic variables, in particular IL-6, CRP and polymorphonuclear elastase levels ($r > 0·75$, $P < 0·001$). There was also a strong correlation between falls in albumin and transferrin concentrations ($r = 0·69$, $P < 0·001$). A weak correlation was found between duration of surgery and IL-6 response ($r = 0·50$, $P = 0·04$), but there were no correlations between pain scores and pulmonary function and the metabolic variables.

Table 1 *Metabolic changes expressed as area under the curve*

	Cholecystectomy		
	Minilaparotomy	Laparoscopic	P*
C-reactive protein (mg/l × h × 10^2)	84 (15–359)	48 (13–365)	0·13
Interleukin 6 (pg/ml × h × 10^2)	135 (66–212)	117 (54–336)	0·76
Fall in albumin (g/l × h × 10)	71 (7–171)	90 (35–166)	0·45
Fall in transferrin (g/l × h)	65 (36–142)	63 (5–145)	0·82
Fibrinogen (g/l × h × 10)	69 (52–111)	70 (49–111)	0·71
Fibrin degradation products (ng/ml × h × 10^3)	68 (34–119)	49 (27–130)	0·25
Cortisol (nmol/l × h × 10^3)	13 (7–30)	15 (7–34)	0·50
Polymorphonuclear elastase (μg/l × h × 10^2)	46 (28–78)	37 (20–112)	0·60
Fall in iron:transferrin ratio (ratio fall × h)	48 (4–96)	43 (−19 to 76)	0·60

Values are median (range). *Mann–Whitney *U* test

Table 2 *Morphine consumption, pulmonary function and pain 24 h after operation*

	Cholecystectomy		
	Minilaparotomy	Laparoscopic	P*
Morphine consumption (mg)	44 (24–62)	16 (10–26)	0·021
Peak expiratory flow rate (percentage of preoperative value)	44 (36–49)	78 (53–80)	0·012
Linear analogue pain score (mm)†	58 (30–85)	37 (30–40)	0·074

Values are median (interquartile range). *Mann–Whitney *U* test; †scale 0–100 mm

Discussion

This study demonstrated a significant metabolic response to laparoscopic and minilaparotomy cholecystectomy, with no significant differences between the two types of surgery. The laparoscopic operation, however, results in less postoperative pain than minilaparotomy cholecystectomy[24], a smaller reduction in pulmonary function after operation, better postoperative oxygen saturation[25] and a more rapid return to normal activity[37]. There were no correlations between postoperative pain and pulmonary function, and the magnitude of the metabolic response; this concords with the finding that elimination of postoperative pain by epidural infusion of bupivacaine does not significantly alter the metabolic response to cholecystectomy[2,4]. Therefore pain after surgery is only one of a number of factors affecting the magnitude of the metabolic response.

The metabolic effect of minilaparotomy cholecystectomy has not been described previously. The present peak CRP response to minilaparotomy was within the range reported after standard open cholecystectomy[17,22,38–42] and the IL-6 response to both operations was similar to that after standard cholecystectomy using the same bioassay[43]. The falls in albumin and transferrin levels and the iron:transferrin ratio were similar to those after standard cholecystectomy[32]. The peak cortisol response to both operations was lower than that reported after standard cholecystectomy in several studies[3,4,42,44]. Three recent papers compared selected aspects of the metabolic response to laparoscopic and standard open cholecystectomy, using historical[38] and non-randomized[39,44] controls. The CRP responses to laparoscopic cholecystectomy reported in two[38,39] were lower than those in the present study. Using an immunoradiometric assay, Joris *et al.*[38] found lower IL-6 levels after laparoscopic cholecystectomy, although measurements were made at only three time points and the control group was historical. Two of these three studies showed a similar cortisol response after open and laparoscopic cholecystectomy[38,44]. Catecholamine changes have not shown a consistent pattern[38,39].

The sequential time course of IL-6, which preceded the rise of CRP and fibrinogen levels, and the strong correlation between these three markers is consistent with this interleukin being the primary stimulus to the acute-phase response[27]. Polymorphonuclear elastase values were raised throughout the postoperative period compared with preoperative levels, but changes were modest compared with those seen in severe sepsis[45]. Although monocytes, endothelial cells and fibroblasts are thought to be the major *in vivo* source of IL-6, some recent evidence suggests that circulating neutrophils contribute significantly to IL-6 production[46]. The strong correlation between changes in IL-6 and polymorphonuclear elastase (which is released by activated neutrophils[33]) and the immediate rise in polymorphonuclear elastase found in the present study are consistent with this hypothesis.

Laparoscopic cholecystectomy does not reduce the metabolic response compared with open surgery, despite less postoperative pain and more rapid recovery. Factors other than metabolic response may be important in determining postoperative recovery.

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Multidrug-resistant colonic cancer cell line LoVoDx is efficiently killed by lymphokine-activated killer cells from patients with carcinoma of the colon

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Multidrug-resistant (MDR^+) cancer cells have the ability to grow in the presence of cytotoxic concentrations of antineoplastic drugs as a result of possessing the transmembrane drug efflux pump p-glycoprotein. The MDR^+ colonic cancer cell line LoVoDx (derived from the drug-sensitive line LoVo) was tested for sensitivity to lymphokine-activated killer (LAK) cell-mediated toxicity. LAK cells were cultured from patients with colonic cancer and from matched controls with benign disorders. LAK cells from patients with cancer were as effective as those from controls in mediating cytotoxicity. The MDR^+ cell line was significantly more sensitive to LAK cell-mediated cell killing than its parental drug-sensitive line LoVo ($P < 0.05$)*. These results indicate a possible role for adoptive immunotherapy in MDR^+ tumours expressing p-glycoprotein.*

Multidrug resistance is the acquisition of resistance to a spectrum of antineoplastic agents by a cell[1] and is frequently associated with expression of p-glycoprotein[1,2]. This is a 170-kDa cell-surface glycoprotein that functions as an energy-dependent drug efflux pump[2,3]. Cells expressing p-glycoprotein have the ability to extrude certain anticancer drugs much more rapidly than those not possessing it, thus minimizing their exposure to the drugs' toxic effects. This phenomenon may limit the effectiveness of treatment in a significant number of tumour types with a drug-resistant clone[3,4]. Therapeutic strategies to circumvent this effect include the use of chemotherapeutic agents not affected by the multidrug resistance phenotype, such as cisplatin or methotrexate, or to utilize agents that reverse multidrug resistance, such as verapamil or cyclosporin analogues[5,6].

Adoptive immunotherapy does not depend on chemosensitivity for antitumour activity[7,8]. Treatment of tumours with a subpopulation of multidrug-resistant (MDR^+) cells with combined chemotherapy and immunotherapy might be more successful if the cells unaffected by chemotherapy were sensitive to cell-mediated cytotoxicity. Although several studies have examined the sensitivity of MDR^+ tumour cell lines to lysis by lymphokine-activated killer (LAK) cells from healthy volunteers[9,10], none has so far addressed the issue of whether these findings apply to patients with tumours. This study examines the ability of LAK cells obtained from patients with colorectal cancer to lyse the human colorectal cancer cell line LoVo and its MDR^+ derivative LoVoDx. The cytotoxicity of effector cells derived from tumour-bearing patients with those from healthy controls is also compared.

Materials and methods

Cell lines

LoVoDx is derived from LoVo that has been subjected to gradually increasing doses of doxorubicin and has developed the MDR^+ phenotype, expressing p-glycoprotein at high levels. LoVoDx was maintained in logarithmic growth in Ham's F12 culture medium plus 100 ng/ml doxorubicin. LoVo and LoVoDx were gifts from Dr M. Grandi (Farmitalia Carlo Erba, Milan, Italy).

CEM is a human T cell leukaemia cell line. CEMV1b is a vinblastine-resistant subline that expresses p-glycoprotein at high levels. CEMV1b was grown in RPMI L654D medium plus vinblastine 100 ng/ml. (CEM and CEMV1b were gifts from Dr S. Brennan, Centocor, Malvern, Pennsylvania, USA.) CEMV1b and LoVoDx were grown in drug-free medium for 3 weeks before being used as targets in cytotoxicity assays to avoid the confounding influence of doxorubicin or vinblastine in the experiment. Using flow cytometry with the C219 monoclonal antibody (Centocor) directed against p-glycoprotein on MDR^+ cells, the cultured cells were found to express the glycoprotein at the same levels, indicating no significant loss of multidrug resistance over this interval.

Interleukin 2-activated killer cells

Peripheral blood lymphocytes were isolated by Ficoll–Hypaque (Pharmacia, Milton Keynes, UK) gradient from venous samples taken from controls and patients with colonic cancer. To generate LAK cells the lymphocytes were cultured in RPMI 1640 enriched with 10 per cent fetal calf serum, 2 mmol/l glutamine, 100 units/ml penicillin and 100 μg/ml streptomycin, at 2×10^6 cells/ml for 3–5 days in the presence of recombinant interleukin (IL) 2 (Eurocetus, Amsterdam, The Netherlands) at a concentration of 1000 units/ml.

Cytotoxicity assay

A standard 4-h ^{51}Cr release assay was used. Target cells were prepared from LoVo, LoVoDx, CEM and CEMV1b cell lines. Some 10^4 ^{51}Cr-labelled cells were placed in each well of a round-bottomed 96-well plate and effector:target ratios from 100:1 to 12·5:1 employed. When 4 h had elapsed, 100-μl aliquots of the supernatant were aspirated and counted in a γ counter. Experimental release was calculated for each sample. The spontaneous release was calculated for wells to which culture medium alone was added and the maximum release calculated for wells to which 5 per cent Lipsol (LIP, Shipley, West Yorkshire, UK) had been added. Percentage specific lysis was calculated according to the formula:

$$\text{Percentage specific lysis} = \frac{\text{experimental release} - \text{spontaneous release}}{\text{maximum release} - \text{spontaneous release}} \times 100$$

CEM and CEMV1b were used for comparison, as previous data showed them to be differentially sensitive to LAK-mediated cytotoxicity. The experiments were carried out in triplicate.

Study population

The patients were immediately preoperative inpatients with primary tumours ($n = 6$) or known postoperative recurrence ($n = 3$). The controls were matched inpatients ($n = 7$) undergoing minor elective surgery for benign disorders.

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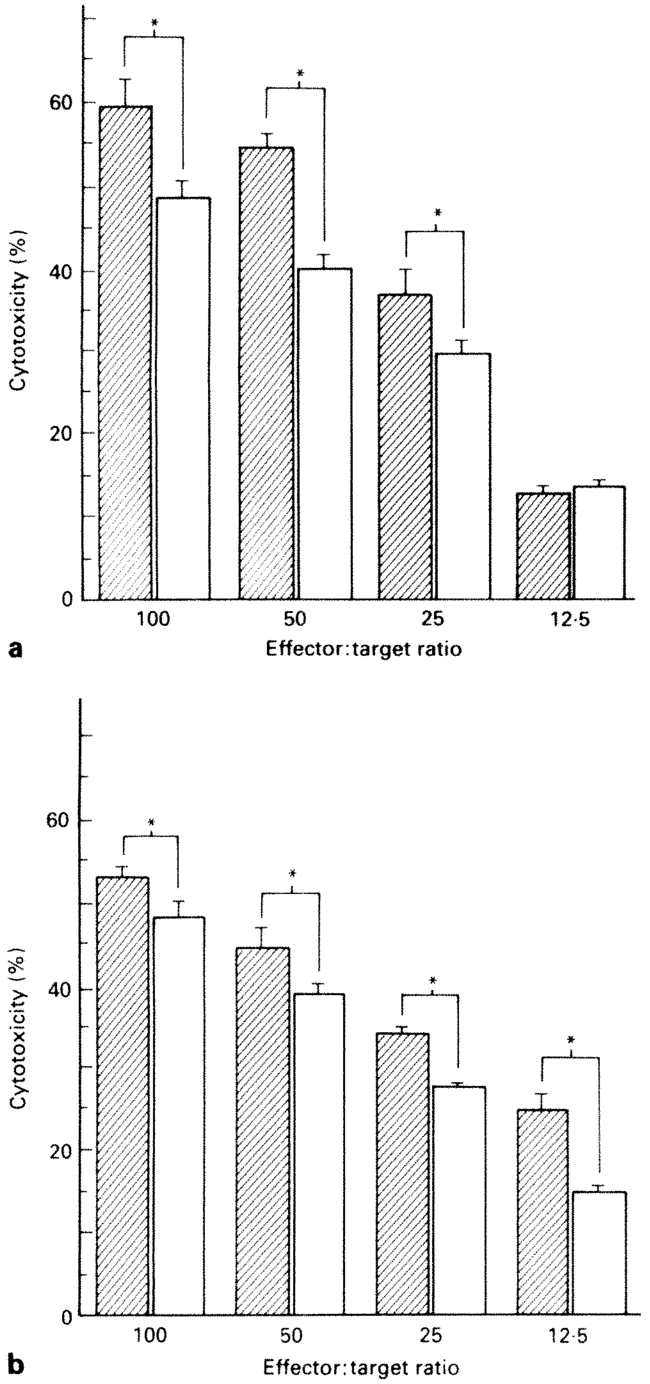

Figure 1 *Mean(s.e.m.) percentage specific lysis of colonic cell lines as assessed by ^{51}Cr-release cytotoxicity assay using lymphokine-activated killer cells from* **a** *patients with cancer and* **b** *controls.* ▨, *Multidrug-resistant LoVoDx;* □, *parental line LoVo.* *P < 0·05 *(two-way ANOVA)*

Statistical analysis

The differences between cell lines, and patients and controls were subjected to two-way analysis of variance and a Duncan's test of individual significance. Results are expressed as mean(s.e.m.).

Results

IL-2-stimulated effector cells mediated a high level of cell killing in both the colonic and leukaemic cell lines. There was a statistically significant higher sensitivity to LAK cell cytotoxicity in MDR$^+$ than MDR$^-$ cells ($P < 0.05$); this was seen in both the leukaemic and colonic cell lines. The LAK cells from patients with cancer were equally effective as those from normal controls. The results of the cytotoxicity assays on the colonic cell lines are shown in *Figure 1* and on the leukaemic lines in *Figure 2*.

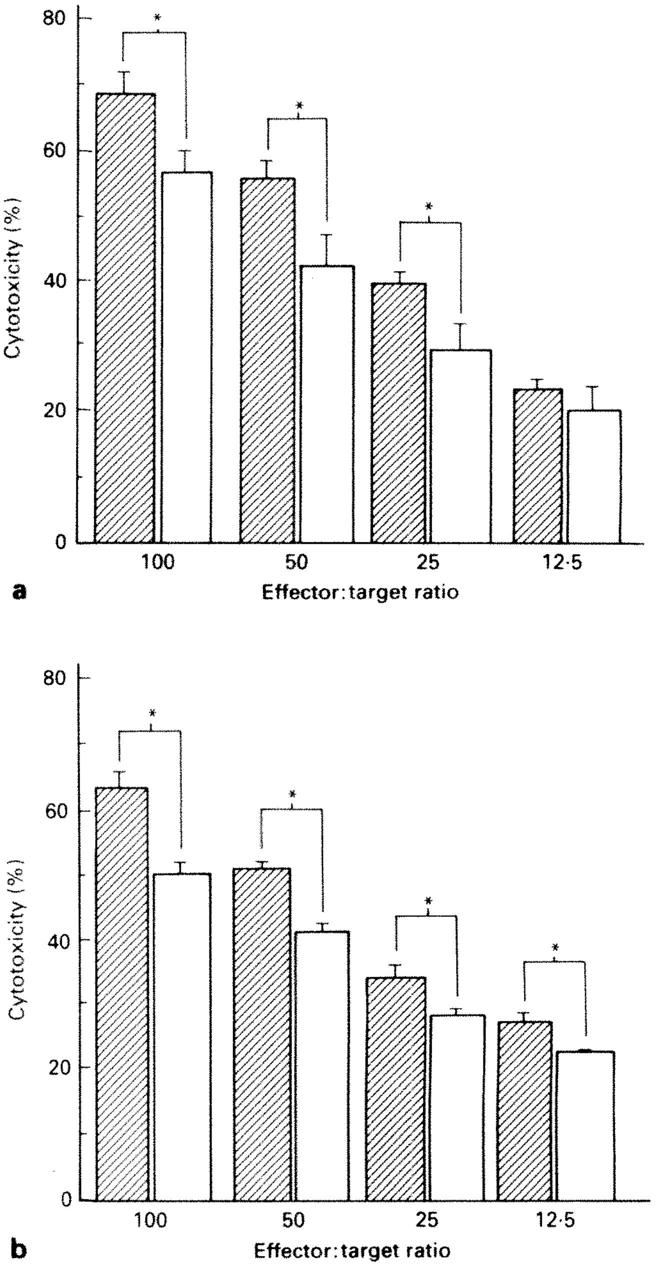

Figure 2 *Mean(s.e.m.) percentage specific lysis of leukaemic cell lines as assessed by ^{51}Cr-release cytotoxicity assay using lymphokine-activated killer cells from* **a** *patients with cancer and* **b** *controls.* ▨, *Multidrug-resistant CEMVlb;* □, *parental line CEM.* *P < 0·05 *(two-way ANOVA)*

Discussion

Multidrug resistance was first described by Juliano and Ling[1], who detected the p-glycoprotein in a Chinese hamster ovary cell line in 1976. The p-glycoprotein is an ATP-dependent active transport system that extrudes certain hydrophobic molecules from the cell[2,3]. In several studies with animal models a combination of chemotherapy with immunotherapy has been shown to produce more effective tumour regression than either alone. MDR$^+$cells may differ from their MDR$^-$ counterparts in their sensitivity to cell-mediated cytotoxic damage[11,12]. The present study assessed the sensitivity to cell-mediated cytotoxicity of a MDR$^-$ cell line and its parenteral MDR$^-$ line, and compared the effectiveness of LAK cells from patients with benign disorders with those from patients bearing a tumour of the same tissue of origin.

The results show that the presence of the multidrug resistance p-glycoprotein on the surface of the LoVoDx cancer cell was associated with an increase in sensitivity to LAK cell cytotoxicity. The mechanism by which this increase in sensitivity occurs is unclear. This study also shows that the phenomenon was present when the cytotoxic cells came from patients suffering the malignancy from which the cell line was derived. Further assessment of this form of therapy in animal experiments and clinical trials may therefore be possible.

Exposure to agents that reverse drug resistance has no effect on the sensitivity to cell-mediated killing[10]. Blocking the extracellular component of p-glycoprotein with a monoclonal antibody, making it less accessible to antigen-recognizing moieties on cytotoxic LAK cells, has no effect on the amount of cell killing achieved[10]. Down-regulating the expression of p-glycoprotein by use of antisense oligodeoxynucleotides to multidrug resistance gene 1 RNA, which causes marked reduction in surface p-glycoprotein levels, has failed to alter the sensitivity of cells to LAK-mediated cytotoxicity[10]. The use of agents that block the pump action of p-glycoprotein, such as verapamil, has failed to produce a change in sensitivity to cell-mediated killing, despite reversing the resistance to cytotoxic drugs[10]. These findings support the view that it is not as a direct result of the expression of p-glycoprotein on the cell surface that MDR^+ cells are more sensitive to cell-mediated cytotoxicity.

The physical properties of MDR^+ cell membranes are different[13] and this may cause increased susceptibility to cytotoxins released by activated killer cells. The level of expression of the surface glycoprotein and its messenger RNA are very high in resistant cell lines and tumours. This utilization of a large part of the cell's synthetic pathways with a superspecialized function might be associated with loss or diminution of other protective mechanisms.

Salmon *et al.*[3] have shown that MDR^+ leukaemia and myeloma cell lines demonstrating acquired multidrug resistance are more sensitive to the toxic effects of recombinant tumour necrosis factor (TNF) in clonogenic assays. The release of cytokines such as TNF by LAK cells may account partly for the increase in sensitivity to LAK-mediated cytotoxicity observed in this set of experiments. The present data show that treatment with immunochemotherapy of tumours containing clones with pleiotropic resistance to chemotherapeutic agents may be of therapeutic benefit.

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Long-term results of a single protocol for thrombolysis in acute lower-limb ischaemia

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In a prospective study, 78 of 157 patients with acute lower-limb ischaemia were considered suitable for thrombolysis. The immediate and 4-year results of 52 patients managed by a single protocol are reported. Of 34 patients alive at 4 years, 23 had limb salvage. Initial treatment produced effective lysis in 38 patients (73 per cent) with significant benefit in 35 (67 per cent); that benefit was sustained for a minimum of 4 years in 30 patients (58 per cent). Seven of the 18 deaths by 4 years occurred within 30 days. Amputation was carried out in six patients within 30 days and in five during the next 4 years. Delayed amputation followed persistent distal occlusion or progression of distal disease. No death or amputation was caused by complication of treatment. In selected patients the risks of thrombolysis can be reduced to an acceptable level by personal supervision and a strict protocol. In survivors, limb salvage is generally sustained for at least 4 years.

About 25 patients from this district of 200000 people present annually with acute limb ischaemia. The early mortality rate commonly exceeds 15 per cent and up to 30 per cent of patients require amputation[1]. Amputation for ischaemia involves high cost, a significant loss of independence, a poor quality of life and shortened survival after operation. Every effort must be made to save the limb in patients with no neurological damage who are likely to survive. Management options include anticoagulation with medical support, surgical intervention and thrombolysis, but the precise indications for each treatment have yet to be defined and outcome is not necessarily improved by increased intervention[2]. The causes of acute ischaemia are changing, with a decline in the incidence of systemic embolism and a rise in the incidence of arterial thrombosis.

This change in the cause of ischaemia, together with new developments in catheters and the advent of new thrombolytic agents, make the design of a controlled trial difficult. Several centres have published early results suggesting an improvement in the effectiveness and safety of thrombolysis as experience increases. These reports of initial success need now to be qualified by an assessment of long-term outcome.

Since 1982, all patients presenting to the Royal Surrey County Hospital with acute limb ischaemia have been assessed by a vascular surgeon (A.E.B.G.) and an interventional radiologist (W.J.W.) who have also carried out all procedures. In 1988, the present authors published a protocol for the safe treatment of acute lower-limb ischaemia with intra-arterial streptokinase and surgery, and described the initial results[3]. The present paper reports a long-term follow-up of that treatment.

Patients and methods

A total of 157 patients with acutely ischaemic limbs admitted between 1982 and the end of 1988 were studied prospectively to establish long-term outcome. Of these patients, 23 (15 per cent) were admitted with an acute white leg, suggesting systemic embolism, and were managed by immediate balloon-catheter embolectomy. Fifty-six patients (36 per cent) presented with subacute arterial thrombosis and were treated with heparin, medical support and elective investigation. The remaining 78 patients (50 per cent) were considered suitable for thrombolysis.

The first 26 patients so treated were the subject of an earlier report while the treatment protocol was being developed[4]. These and the next 44 patients were reported[3] in 1988. A further eight patients have now been added to the 44 previously reported. All 52 patients, who are the subject of the present report, have been treated with a single (Guildford) protocol and all survivors followed for a minimum of 4 years. Follow-up ranged from 0 to 89 months; the mean for all 52 patients was 45·1 months.

Data were obtained from clinical follow-up except for two patients. One of these was treated for peripheral arterial thrombosis after a myocardial infarction. The patient's limb was saved by thrombolysis and an irregular popliteal artery, thought to be the cause of the thrombosis, was noted. He was treated by anticoagulation and subsequently left hospital alive but cannot now be traced. The second patient lost to follow-up underwent satisfactory lysis for an arterial thrombosis. Lysis was followed by a successful femoropopliteal bypass, which is known to have remained patent for at least 2 years until contact was lost.

Results

Lysis was considered effective, removing between 70 and 100 per cent of the obstruction (as previously described), in 38 patients (73 per cent) and ineffective in 14 (27 per cent). In 35 patients (67 per cent) thrombolysis was judged to have conferred unique benefit since an underlying correctable lesion was demonstrated and corrective therapy was effective.

Mortality

Over the 4-year period 18 patients (35 per cent) died, seven (13 per cent) within the first 30 days (*Table 1*). Analysis of the cause and timing of death showed that in only three cases could mortality be attributed directly to unrelieved limb ischaemia and that these deaths occurred within the first 30 days. The cause and time of late death are shown in *Table 2*. The majority of patients in whom lysis was effective survived with limb

Table 1 *Causes of early death (within 30 days of treatment) in 52 patients*

Patient no.	Cause of death	Time after treatment
1	Peripheral ischaemia	2 days
2	Perforated colonic diverticulum	10 days
3	Bronchopneumonia after amputation	13 days
4	Pulmonary embolism after amputation	3 weeks
5	Stroke	3 weeks
6	Pneumonia	3 weeks
7	Myocardial infarction	4 weeks

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Table 2 *Causes of late death (30 days to 4 years after treatment) in 52 patients*

Patient no.	Cause of death	Time after treatment
8	Pneumonia	2 months
9	Myocardial infarction	1 year 0 months
10	Myocardial infarction	1 year 2 months
11	Myocardial infarction	2 years 3 months
12	Myocardial infarction	2 years 11 months
13	Congestive heart failure	3 years 0 months
14	Pneumonia	3 years 6 months
15	Congestive heart failure	3 years 10 months
16	Colonic carcinoma	4 years 3 months
17	Acute renal failure	4 years 8 months
18	Multiple strokes	6 years 10 months

Table 3 *Other treatment required after thrombolysis in 52 patients*

After effective lysis ($n = 38$)	
Anticoagulation	9 (17)
Angioplasty	9 (17)
Angioplasty and anticoagulation	7 (13)
Surgery	7 (13)
Angioplasty and surgery	6 (12)
After ineffective lysis ($n = 14$)	
None	4 (8)
Anticoagulation	1 (2)
Surgery	9 (17)

Values in parentheses are percentages

Table 4 *Operations after thrombolysis in 52 patients*

	After effective lysis ($n = 38$)	After ineffective lysis ($n = 14$)
Endarterectomy, surgical angioplasty	1	3
Bypass graft	4	2
Removal of clot or debris	8	4
Total	13	9

Table 5 *Causes of occlusion diagnosed after thrombolysis in 52 patients*

Arterial thrombosis	33 (63)
Embolism	8 (15)
Occluded graft	7 (13)
Uncertain	4 (8)

Values in parentheses are percentages

salvage to die from another cause at a later date. There were no deaths attributable to stroke, haemorrhage or other complication of thrombolysis.

Amputation

Eleven patients underwent amputation: six (12 per cent) had surgery within 30 days and five (10 per cent) at a later time. Of these five, there was evidence of progression of distal disease in three (who underwent amputation at 3 months, 3 months and 2 years 8 months respectively) and of unrelieved microembolic occlusion caused by popliteal artery aneurysm in two (who underwent amputation at 11 months and 1 year 9 months respectively). In these last two patients distal amputation was required despite successful proximal bypass.

Further interventions

These are shown in *Tables 3* and *4*. Complications of the treatment were divided into major and minor, as previously, and there were two complications of angioplasty following thrombolysis.

Major complications

One patient developed temporary diplopia and ptosis associated with a parieto-occipital haematoma proven on computed tomography. The patient made a full recovery. A second patient sustained superficial femoral artery perforation after successful lysis. This was repaired with a vein patch.

Minor complications

These consisted of two allergic reactions, one acute confusional state, one large groin haematoma with abscess formation and a second large groin haematoma, which produced local pressure thought to be responsible for a proven deep vein thrombosis.

Complications of angioplasty after thrombolysis

One patient had thrombosis of a reversed saphenous vein graft and, after successful lysis, had the graft ruptured during attempted dilatation of a stricture in its upper third. The graft was replaced by a synthetic conduit which also failed and the patient came to amputation. There was one case of embolization of atheromatous debris following angioplasty; this produced no lasting clinical effects. No deaths or amputations could be attributed directly to a complication of therapy. The diagnosis of the cause of the occlusion made after thrombolysis is shown in *Table 5*.

Discussion

Changing patterns of acute limb ischaemia

Episodes of enthusiasm and disappointment have marked the development of thrombolysis[5] over the past 30 years. Postangioplasty thrombosis, and new thrombolytic drugs and techniques of administration have led to a resurgence of interest. This is particularly so in the difficult problem of acute limb ischaemia, the ideal management of which has yet to be agreed. Significant benefit accrues simply by efficient medical care and anticoagulation therapy, but the additional benefits from surgery, interventional radiology, thrombolysis – or all methods in combination – have not been measured. The decline in the incidence of rheumatic heart disease and systemic embolism in younger patients during the past two decades has been balanced by a significant increase in the number of elderly patients at risk from atherosclerosis and arterial thrombosis. The pathology and outcome for patients with systemic embolism are substantially different from those of patients with native artery thrombosis[5]. The risk of systemic embolism is to life rather than limb (mortality rate 17 per cent, amputation rate 13 per cent), whereas for intra-arterial thrombosis the mortality rate is less (9 per cent) but the amputation rate higher (28 per cent). These figures represent short-term results (within 30 days) and seriously underestimate the threat to the untreated limb after arterial thrombosis. The classical acute white leg resulting from cardiac embolism is now rare and the majority of patients presenting with an ischaemic limb suffer from spontaneous arterial thrombosis, thrombosis following an interventional radiological procedure, or failure of an arterial graft.

The fundamental question is whether the results of thrombolysis in acute ischaemia are now superior to those of the simpler management of medical support, heparin and elective investigation. Positive evidence for the effectiveness and safety of elective surgical management in the USA has been presented[6] but in Guildford elderly patients predominate, many of whom are high-risk women[1] with end-stage disease; direct comparison is difficult. The present authors have responded to current uncertainty about the best management by an early study of low-dose intra-arterial streptokinase and in 1985 published the first account in the UK of this therapy for acute lower-limb ischaemia[4]. From that experience, a single treatment protocol was defined[3]. The management depends on the personal involvement of the same vascular surgeon and interventional radiologist who also carry out all the interventional procedures. The present paper records that experience and is unique in that all patients treated suffered acute ischaemia and all have been studied prospectively for at least 4 years.

Advantages of low-dose intra-arterial infusion

Earlier reports of thrombolysis using systemic streptokinase at high dosage and for long periods showed effective dissolution of clot but a prohibitive risk of haemorrhage and stroke. Modern imaging techniques and catheters have for a decade made the local intra-arterial route the approach of choice. Lower doses and shorter infusion times have reduced complications while permitting precise monitoring of effect by repeat arteriography. New agents, including tissue plasminogen activator (tPA) and urokinase, have been used; both high- and low-dose regimens have been recommended[7,8]. Sometimes these are supplemented by mechanical disruption and clot suction, and in some hospitals all these methods have been tried. Having established a protocol that appeared to be reasonably safe and inexpensive, and one that could be managed conveniently within the limited facilities of a district general hospital, the authors have deliberately chosen to continue with low-dose intra-arterial infusion of streptokinase in all patients in whom allergy or recent exposure did not contraindicate its use. Patients sensitized to streptokinase are in our experience still rare. The alternative of low-dose intra-arterial tPA has been required in fewer than 5 per cent of patients, none of whom is included in this series. The more widespread use of streptokinase for myocardial infarction may change this ratio by increasing the incidence of allergy, but the improved purity of modern streptokinase and its low cost are significant advantages. Recent evidence suggesting that it may be as effective as tPA and also have enhanced safety[9,10] makes the authors reluctant to use the more expensive agent as a first choice.

Urokinase, while commonly used in the USA[11], is very expensive and has no specific advantage with respect to lysis itself, although it does offer protection against allergic reaction. The authors' experience with streptokinase has shown that low-dose infusion for a period of 24–36 h yields greatest benefit with minimal risk and this series is the largest and longest so far reported using a single protocol. Other centres, particularly regional vascular units with larger numbers to treat, have made valuable contributions to the understanding of the effects of different drugs, dosages and methods of administration[12,13] but practice varies widely throughout the country[14] and direct comparison with the present work is difficult. In acute ischaemia, streptokinase and tPA have similar rates of lysis and complications[15]. It has been suggested that tPA may be superior to streptokinase because of more rapid lysis[16] but that evidence must be viewed cautiously, bearing in mind the prolonged and perhaps ineffective lysis experienced by these authors using streptokinase early in their series. The present authors have previously identified prolonged and ineffective infusion as significant risk factors for haemorrhage and failure. With increasing experience, lysis times tend to fall and the risks of haemorrhage, stroke and failure are thereby reduced.

The effectiveness of an infusion in removing clot has been described in terms of complete or partial lysis. It is well to remember that radiological distinction between persisting clot and atheroma is imprecise, and that some failures of lysis are certainly caused by atheromatous debris that requires surgical removal. It should also not be forgotten that some patients in whom lysis is effective will none the less lose their limb or die; successful lysis does not necessarily mean a successful clinical result.

Appreciating the hazards of prolonged infusion, many recent reports[17] have favoured a higher dose bolus technique using streptokinase or tPA, while observing the effects directly over periods of 30–60 min. The effect is often dramatic; it may extend the repertoire of thrombolysis to patients with even more acute and severe ischaemia, and may allow immediate intervention for clot suction and angioplasty. This may be a particularly useful method where dedicated radiological facilities are constantly available and there is clinical urgency, but the safety of high-dose bolus regimens has yet to be established. The present authors are reluctant to change their protocol in any way that might increase the risk of stroke. While there may be a role for a single higher dose bolus when the catheter is first positioned, to check that lysis is possible and thereby avoid the 12-h low-dose trial infusion, the safety of high-dose treatment must be proved. We believe that low-dose intra-arterial streptokinase infusion with check radiographs every 12 h offers the advantages of proven safety, organizational convenience and economy.

What other measures are required?

Throughout the authors' experience thrombolysis has been regarded mainly as a valuable diagnostic aid, which may sometimes provide a complete treatment but more usually will reveal an underlying cause that then requires angioplasty or surgical correction. They have found that thrombolysis alone is sufficient in fewer than 20 per cent of patients.

Assessment of long-term results

The ultimate question to be asked of any medical intervention is whether it improves the length and quality of life at reasonable cost. Reporting mortality and amputation rates at 30 days is inadequate, but there are very few accounts in which later outcome is recorded. In some studies, results are confused by the mixture of acute, subacute and chronic ischaemia[18] and in some by uncertainty about the severity of lesions treated[19,20]. Some reports of surgical results do not define primary and secondary patency[21].

Comparison of outcome in patients with high risk is difficult because the rate of attrition of those with critical ischaemia is high. At 5 years only 40 per cent will survive, compared with 70 per cent of those with claudication[22]. Life-table analysis suggests objectivity[23] but may be inappropriate, since death in patients with peripheral vascular disease is usually from causes other than the peripheral ischaemia that is being assessed. Similarly, it is of little value to report 'patency rates' that have not been proved by repeat arteriography, since it is known that reocclusion can occur without clinical deterioration. Surrogate indicators such as limb salvage should not be used to indicate patency of a treated vessel. The durability of any intervention requires unambiguous proof by arteriography or duplex ultrasonography before patency can be claimed. This study, therefore, reports only the definite endpoints of death and amputation.

Need for controlled clinical trials

Randomized controlled trials are urgently needed since current reports include patients of widely differing degrees and duration of ischaemia, and results from centres where surgery may be the preferred or only option. Some studies of thrombolysis have excluded patients presenting within 24 or 48 h of the onset of ischaemia, all of whom were diverted to surgical care.

In Guildford all patients except those with acute white leg have been considered for thrombolysis. It is concluded that thrombolysis offers the prospect of saving the acutely ischaemic limb of the elderly arteriopathic patient until probable death from another cardiovascular cause; an evaluation of exactly when it is the most effective treatment now needs to be made.

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Low-dose aspirin fails to inhibit increased platelet reactivity in patients with peripheral vascular disease

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A study was performed to evaluate the effect of low-dose aspirin (75 mg/day) on platelet reactivity in patients with peripheral vascular disease. Platelet function was measured in 31 patients with advanced peripheral vascular disease requiring surgery. Shear-induced haemostasis and collagen-induced thrombus formation were used as indicators of platelet reactivity. They were measured in non-anticoagulated fresh whole blood samples ex vivo *using a haemostatometer. Results were compared with those from 30 age- and sex-matched controls. Shear-induced haemostasis and collagen-induced thrombus formation were also measured in 18 of the 31 patients before the start of aspirin administration (before operation) and 1 week after surgery. Patients with advanced peripheral vascular disease were found to have increased platelet reactivity with a mean(s.e.m.) shear-induced haemostasis index of 1977(180) mmHg s compared with a control value of 3161(234) mmHg s ($P < 0{\cdot}001$) and a mean(s.e.m.) collagen-induced thrombus formation index of 3980(460) mmHg s compared with a control value of 5350(420) mmHg s ($P = 0{\cdot}02$). Perioperative low-dose aspirin failed to inhibit platelet function in patients with peripheral vascular disease.*

Platelets are thought to play a pivotal role in the pathogenesis of human atherosclerosis[1] and in restenosis after vascular surgery or angioplasty. Antiplatelet agents have been shown to protect against stroke[2] and adverse cardiovascular events[3]. Aspirin is one of the most extensively studied of these agents and it may play an important role in modifying responses to the insertion of vascular grafts[4,5] or to balloon angioplasty[6,7]. However, the data remain confusing, with a recent study showing protective effects of aspirin in the coronary and cerebral circulations, but not in peripheral vein bypass grafts[8].

Aspirin has been shown to reduce smooth muscle cell proliferation in an animal model[9]. The mechanism is thought to involve the inhibition of platelet activation and degranulation. It is used by vascular surgeons in the management of peripheral vascular disease, but the rationale for its use is not well defined and dosage regimens are arbitrary. This study was undertaken to examine the effect of a single-dosage regimen of aspirin at 75 mg/day. This dose was chosen as it is that given to patients in this unit after angioplasty[10].

Patients and methods

Study population

Thirty-one symptomatic patients with peripheral vascular disease were studied before they took any aspirin. Eighteen of this group underwent a procedure to treat peripheral vascular disease after starting aspirin 75 mg/day on the night before surgery. They were also studied a second time 1 week after the procedure. The only other drug used in this study was heparin, which was given during (5000 units) and after (5000 units subcutaneously twice daily) operation until the patient was mobile. No patient was given heparin for more than 4 days and repeat platelet studies were carried out at least 7 days after surgery. The patient group was compared with an age- and sex-matched population of 30 controls (*Table 1*). The controls were not diabetic, had no history of heart disease or claudication and had a palpable dorsalis pedis pulse.

Measurement technique: haemostatometry

Blood was taken from an uncuffed vein into a syringe and measurements obtained immediately on fresh non-anticoagulated samples. Shear-induced haemostasis and collagen-induced thrombus formation were measured using a haemostatometer. These methods have been described and validated in relation to the pathogenesis of coronary thrombosis[11,12]. The coefficients of variation of repeated measurement of shear-induced haemostasis and collagen-induced thrombus formation over a 2-year period in a single individual were 14 and 8 per cent respectively.

Shear-induced haemostasis. The release of adenosine 5′-diphosphate from platelets and red blood cells, and the generation of thrombin, are the major mediators of the shear-induced platelet aggregation that follows breach of a blood vessel wall. Shear-induced haemostasis was measured by producing a standard 'bleeding' stimulus in a polyethylene tube. Immediately after venesection, non-anticoagulated blood was perfused through polyethylene tubing at a constant pressure of 60 mmHg. Once a steady state was achieved, which took less than 2 min, a hole of known dimension was punched in the tube with a fine needle. This resulted in 'bleeding' into a surrounding bath of oil. The blood loss led to a rapid decrease in pressure in the system. As platelets plugged the hole, the pressure in the system recovered and was continuously monitored. The recovery phases have been well characterized[13] and can be used as a measure of platelet reactivity in response to a standard initial shear stress, calculated to be 32 N/m². Reactivity was measured as an integral of change in pressure against time. The faster the pressure rise, the smaller the number generated and the more reactive the platelets (*Figure 1*).

Table 1 *Comparison of the patient group with age- and sex-matched controls*

	Mean(s.e.m.) age (years)	Sex ratio (M:F)
Controls ($n = 30$)	64·6(1·7)	21:9
Patients ($n = 31$)	67·6(1·6)	23:8

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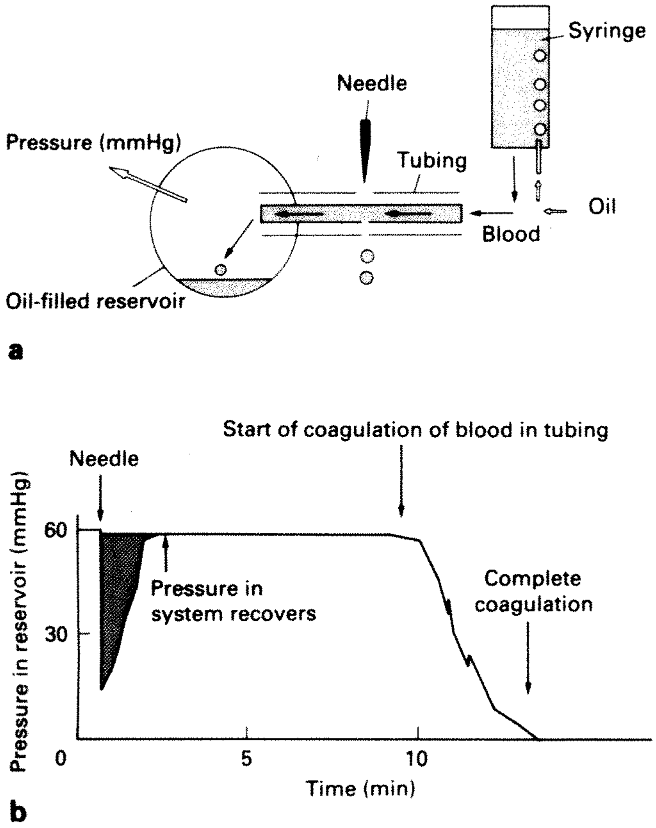

Figure 1 **a** *Schematic diagram of the shear-induced haemostasis test. Blood is perfused through polyethylene tubing from a syringe into an oil-filled reservoir. The tubing is pierced with a needle to induce 'bleeding' and haemostatic platelet plug formation in the holes. The reaction is monitored by pressure changes measured distally in the reservoir.* **b** *Changes in pressure with time in shear-induced haemostasis. The initial pressure is 60 mmHg. This falls sharply following needle puncture of the tubing and 'bleeding' through the holes. As platelet plugs are formed, the pressure recovers to its original value and flow of blood is restored in the tubing. The speed at which this occurs gives a measurement of the platelet reactivity in response to shear stress. Subsequently the pressure falls again as a result of complete coagulation of the blood in the tubing. The shaded area gives an index of platelet reactivity due to shear stress, expressed as an integral of pressure with time. The lower the value, the more reactive the platelets*

Collagen-induced thrombus formation. A second sample of blood was perfused through an identical piece of polyethylene tubing, which contained a standard length of catgut within its lumen. The pressure in the tubing was measured at a point distal to the collagen. As a platelet plug formed on the catgut and occluded the lumen, the measured pressure fell. This change in pressure was continuously monitored. Reactivity was measured as an integral of pressure change with time; as for shear-induced haemostasis, the more reactive the platelets, the smaller the measurement obtained (*Figure 2*).

Statistical analysis

Values are expressed as mean(s.e.m.). Statistical analysis for differences between groups was performed using Student's *t* test. For differences between preoperative and postoperative measurements a paired *t* test was used.

Results

Shear-induced haemostasis and collagen-induced thrombus formation in blood samples from patients with peripheral vascular disease and age-matched controls are shown in *Figure 3*. Patients with peripheral vascular disease had significantly more reactive platelets than controls as measured by both haemostatometer tests. After surgery, in the subgroup of 18 patients, aspirin 75 mg/day failed to reduce platelet reactivity (*Figure 4*). Although there was a trend indicating that platelets were more reactive after operation, this was not statistically significant.

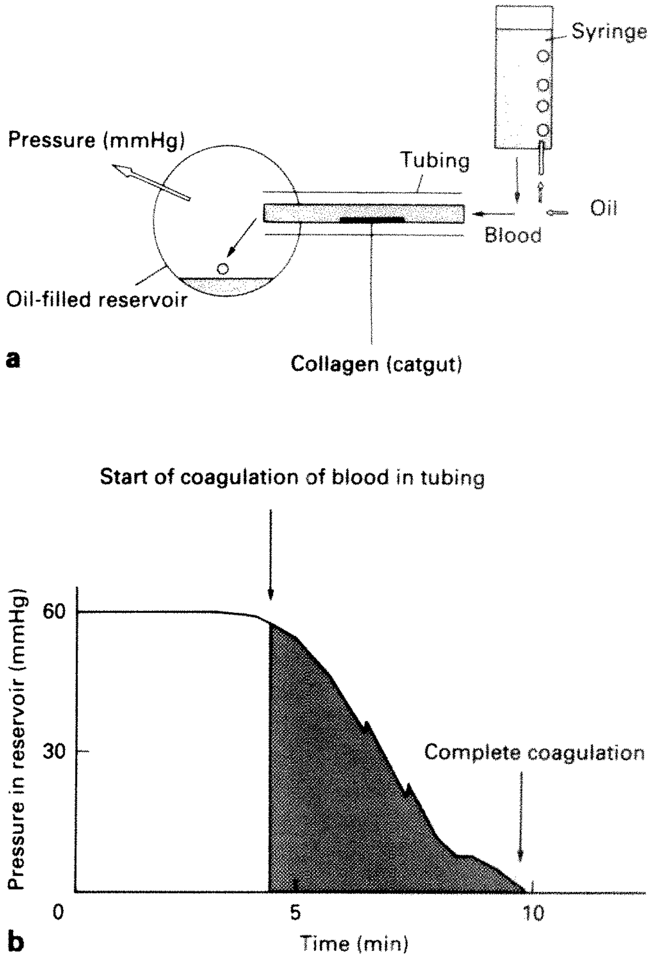

Figure 2 **a** *Schematic diagram of the collagen-induced thrombus formation test. Blood is perfused through polyethylene tubing from a syringe into an oil-filled reservoir. The tubing contains a standard sized piece of catgut. Platelets adhere to the catgut and block the tubing. The reaction is monitored by pressure changes measured distally in the reservoir.* **b** *Changes in pressure with time in collagen-induced thrombus formation. The initial pressure is 60 mmHg; as platelets adhere to the catgut and occlude the tubing, the pressure measured distally falls. The speed at which this occurs gives a measurement of the platelet reactivity in response to collagen-induced thrombus formation. The shaded area gives an index of platelet reactivity due to collagen-induced thrombus formation. The lower the value, the more reactive the platelets*

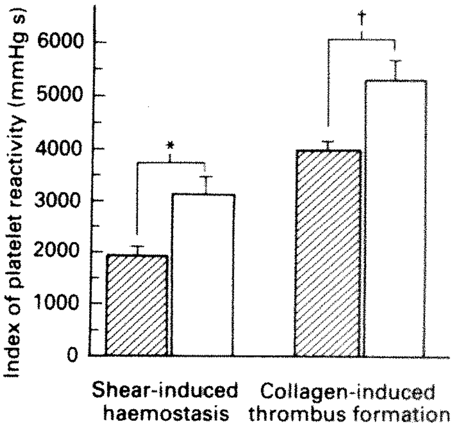

Figure 3 *Results of platelet reactivity to shear-induced haemostasis and collagen-induced thrombus formation in patients with peripheral vascular disease* (▨) *and age-matched controls* (☐). *Values are mean(s.e.m.).* *P < *0·001;* †P = *0·02* (*Student's* t *test*)

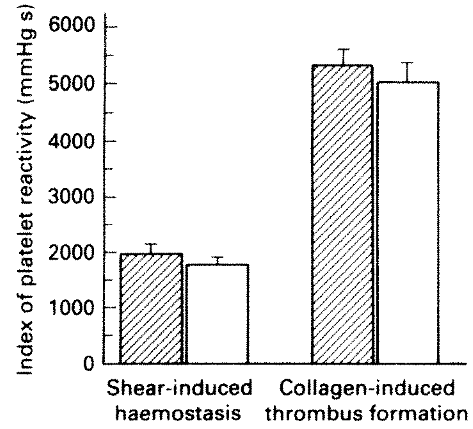

Figure 4 *Results of platelet reactivity to shear-induced haemostasis and collagen-induced thrombus formation measured before* (▨) *and after* (☐) *surgery. Values are mean(s.e.m.). Patients* (n = *18*) *received aspirin 75 mg/day. No change was found in platelet reactivity after administration of low-dose aspirin* (*75 mg/day*) *for 1 week*

Discussion

This study shows that patients with peripheral vascular disease have more reactive platelets than an age- and sex-matched population. This is similar to the prothrombotic tendency previously found in atherosclerotic patients after myocardial infarction[14] and in those studied 3 months following coronary artery bypass grafting[13].

The interaction of platelets with the damaged vessel wall makes a significant contribution to thrombus formation[15,16]. Release of growth factors[17] stimulates smooth muscle cell migration[18] and contributes to the myointimal hyperplasia[19] that follows percutaneous transluminal angioplasty and bypass grafting. Platelets are activated by changes in shear stress within the vessel after bypass, or by exposure of collagen in the subendothelium following the splitting of atherosclerotic plaque by angioplasty[15]. Agents that decrease platelet responses to abnormal shear forces and exposed collagen should decrease thrombus generation and reduce subsequent smooth muscle cell proliferation generated by the release of platelet mitogens. Aspirin is a potent inhibitor of platelets, with demonstrable effects on the cardiac and cerebral circulations in low doses. Its propensity to cause gastrointestinal side-effects, particularly in the elderly, led to use of a low dose (75 mg/day) in patients undergoing angioplasty in this unit. This study establishes that this dosage has no significant effect on platelet reactivity and we advise against the use of such a low dose.

The thrombotic status of patients (n = 294) taking aspirin 75 mg/day 3 months after coronary artery bypass surgery has previously been reported[13]. Ninety of these patients had significantly enhanced platelet reactivity and were advised to increase the daily aspirin dose from 75 to 300 mg. When they were retested 1 month later, it was found that raising the daily dose of aspirin significantly increased the antiplatelet effect measured by the shear-induced haemostasis test[13] (*Figure 5*). We recommend that aspirin be given in a dose of 300 mg/day to patients undergoing peripheral vascular surgery or angioplasty. Whether a correlation between platelet reactivity and subsequent restenosis can be established remains to be determined.

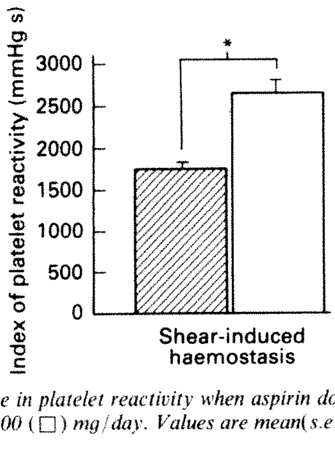

Figure 5 *Change in platelet reactivity when aspirin dose was increased from 75* (▨) *to 300* (☐) *mg/day. Values are mean(s.e.m.).* *P < 0·001 (*Student's* t *test*)

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Changing trends in the management of lower-limb ischaemia: a 17-year review

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Over a 17-year period, 2930 vascular procedures were performed for chronic lower-limb occlusive disease. During this time, the total vascular surgical workload rose significantly as a result of an increase in the rates of arterial reconstruction and percutaneous transluminal angioplasty. Although the major lower-limb amputation rate did not change significantly, there was a decrease in the above- to below-knee ratio. In addition, there were significant increases in the percentage of patients treated over the age of 75 years and the proportion of attempted revascularizations before amputation. The mortality rates for arterial reconstruction, percutaneous transluminal angioplasty and amputation did not change significantly during the study period. The duration of hospital stay increased significantly for patients undergoing amputation and decreased significantly for those receiving arterial reconstruction.

The treatment of lower-limb ischaemia secondary to occlusive arterial disease represents a major part of the workload of vascular surgeons in the UK. During the past two decades, the treatment options available for these patients have increased dramatically. Reconstructive vascular surgery has become widely established as a result of advances in preoperative assessment, anaesthesia, surgical technique and postoperative care that have developed alongside rapid progress in design and manufacture of prosthetic grafts. A major advance occurred in the late 1970s with the introduction of percutaneous transluminal angioplasty (PTA)[1,2], which has become widely established for the treatment of peripheral vascular disease. The indications for surgical and/or radiological intervention in patients with lower-limb occlusive arterial disease have widened with the advent of these new techniques. This paper assesses the changing trends in the management of lower-limb ischaemia in a district health authority over the 17-year period 1974–1990.

Patients and methods

There are three hospitals in the Leicestershire Health Authority that provide vascular services: Leicester Royal Infirmary, Leicester General and Glenfield General. Although vascular surgery was available in Leicester before 1974, it developed rapidly from 1974 onwards following the opening of Leicester Medical School and the University Department of Surgery. At present, vascular services in Leicester are provided by four surgeons: two at the Royal Infirmary, and one each at Leicester General and Glenfield General. PTA was introduced in 1982 and is now available at all three hospitals. The population of Leicester during the period of the present study increased from 829 100 in 1974 to 897 700 in 1990.

The data for this study were obtained from the Hospital Activities Analysis database of the Leicestershire Health Authority from 1974 to 1987 and the Trent Regional Information System from 1987 to 1990. Data were complete for each year except between September 1986 and April 1987 for which no data were available. The two databases contain information on all patients discharged from the hospitals that serve the Leicestershire Health Authority, and each patient is coded according to diagnosis and treatment. The diagnosis codes are based on the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM) and the treatment codes are based on the Office of Population Censuses and Surveys (OPCS) classification of surgical operations, second, third and fourth revisions. The databases provide information on patient name, age, sex, length of hospital stay, discharge and mortality.

Using the two databases, OPCS treatment codes and ICD codes, discharge information was obtained on all patients with chronic occlusive peripheral vascular disease who underwent lower-limb arterial reconstruction (including abdominal aortic procedures), PTA of the lower-limb vessels or major lower-limb amputation (above- or below-knee) between 1974 and 1990. Initially the OPCS treatment codes were used to identify all patients who underwent lower-limb vascular reconstruction (including abdominal procedures), angioplasty or amputation. The search-profile criteria are shown in *Table 1*. To include only patients with chronic lower-limb occlusive disease, those who did not have the ICD codes shown in *Table 2* were excluded. In addition, patients with venous, lymphatic, inflammatory, soft tissue and bone disorders were excluded, as were those with arterial trauma or aneurysmal disease who had the ICD codes shown in *Table 3*.

Data validation

To check the accuracy of the Hospital Activities Analysis data and their usefulness for identification of patients with chronic lower-limb occlusive peripheral vascular disease, the 1990 discharges from the Leicester Royal Infirmary identified by the Hospital Activities Analysis

Table 1 *Office of Population Censuses and Surveys codes used to identify patients undergoing lower-limb arterial reconstruction, percutaneous transluminal angioplasty or major amputation*

OPCS code	Operation
5524	Bypass operation of abdominal vessels
8841	Bypass graft of artery
8819	Endarterectomy of peripheral vessels
8842	Repair of artery by tissue graft
8844	Repair of artery, excision with anastomosis
8845	Repair of artery by suture
8871	Percutaneous transluminal angioplasty
8711	Amputation of lower limb at neck of femur
8712	Amputation of lower limb above knee
8718, 8719	Amputation of lower limb through thigh
8713, 8714, 8728, 8729	Amputation of lower limb through knee
8738, 8739	Amputation of lower limb through lower leg

Table 2 *International Classification of Diseases, ninth revision, codes used to identify patients with lower-limb peripheral vascular disease*

ICD-9 code	Disease classification
440	Atherosclerosis
443	Other peripheral vascular disease
443.9	Unspecified arterial disease
459	Unspecified disorders of the cardiovascular system
707	Chronic ulcer of skin
785.4	Gangrene

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Table 3 *International Classification of Diseases, ninth revision, codes used to exclude patients undergoing a vascular procedure for an indication other than chronic lower-limb occlusive disease*

ICD-9 code	Disease
170	Malignant tumour of bone
171	Malignant tumour of connective tissue
213	Benign neoplasm of bone
342	Hemiplegia
410	Myocardial infarction
414	Ischaemic heart disease
436.9	Cerebrovascular accident
441	Aortic aneurysm
442	Other aneurysm
451	Thrombophlebitis
454	Varicose veins
457	Lymphatic disorders
680–686	Local infections
730	Osteomyelitis
740–759	Congenital abnormalities
799	Ill defined causes of mortality
800–900	Trauma
901–904	Arterial injury
909	Late effects of injury
940–950	Burns
997, 998	Complications not elsewhere classified

data were compared with those identified by the Royal Infirmary vascular audit. The overall accuracy of the Hospital Activities Analysis data was 80 per cent.

Statistical analysis

To standardize the data in terms of age and sex for the three procedures, the number of vascular reconstructions and amputations for the years 1974–1990 inclusive, and the number of angioplasties for the years 1982–1990 inclusive were arranged into quinary bands for age and sex for each year. For the years 1986 and 1987, data were for 8 months of the year rather than the full year. It was assumed that there were no seasonal effects on the number of procedures, and the figures for these years were multiplied by 1·5 to produce estimated rates for the full calendar year. The rates of the procedures for each year were calculated by using the mid-year estimated resident population for Leicestershire, for the relevant year, as the denominator. Adjustments for age and sex were made by direct standardization using the 1981 census figures for Leicestershire for people aged 20 years and over as the standard population. Differences in the rates of variables with time were analysed by linear regression with year as the independent variable and rate as the dependent variable. In addition, continuous variables were analysed using the Mann–Whitney *U* test and discrete variables with the χ^2 test.

Results

During the 17-year period from 1974 to 1990, 2930 vascular procedures were performed for chronic occlusive disease of the lower limb: 1095 arterial reconstructions, 677 PTAs and 1158 major lower-limb amputations.

Standardized rates of procedures

The total vascular workload and the standardized rates of arterial reconstruction, PTA and amputation are shown in *Figures 1–4*. All data are fitted with linear regression lines. The rate of all procedures (*Figure 1*), which represents the total vascular workload in Leicestershire, has increased significantly over the study period ($r^2 = 0{\cdot}72$, $P < 0{\cdot}001$). Similarly, the rates of arterial reconstruction (*Figure 2*) and PTA (*Figure 3*) have also increased significantly ($r^2 = 0{\cdot}89$, $P < 0{\cdot}001$ and $r^2 = 0{\cdot}59$, $P < 0{\cdot}001$ respectively). The rate of major lower-limb amputation (*Figure 4*) has fallen but this decrease is not statistically significant ($r^2 = 0{\cdot}09$, $P = 0{\cdot}25$).

Above- to below-knee amputation ratio

Although the total amputation rate did not fall significantly over the 17-year period, there was a change in the level of amputation. The ratio of above- to below-knee amputations is shown in *Figure 5*; this demonstrates a significant fall over the study period ($r^2 = 0{\cdot}51$, $P = 0{\cdot}001$).

Patients undergoing attempted revascularization before amputation

The percentage of attempted arterial reconstructions or PTAs before major lower-limb amputation was performed at the same hospital admission is shown in *Figure 6*. There has been a significant increase in the number of attempted revascularizations before amputation ($r^2 = 0{\cdot}75$, $P < 0{\cdot}001$). The number

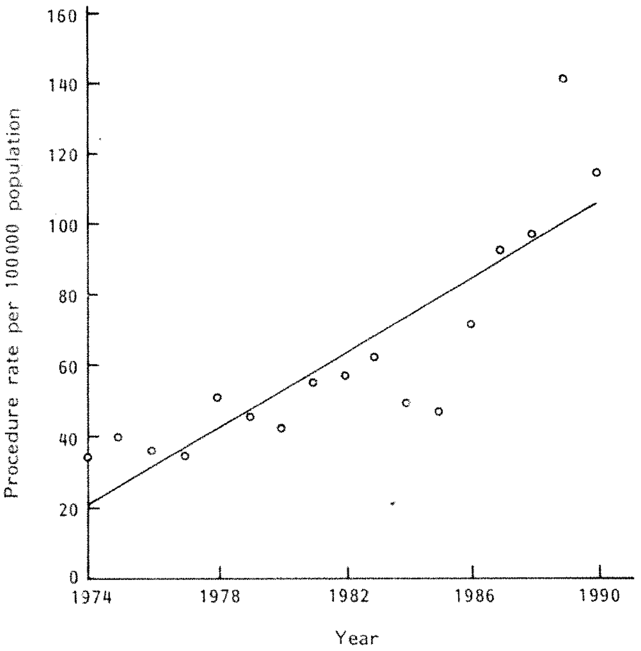

Figure 1 *Total vascular workload for lower-limb ischaemia. Data are presented as age- and sex-standardized rates for all procedures (arterial reconstruction, percutaneous transluminal angioplasty and major lower-limb amputation) per 100 000 population of Leicestershire* ($r^2 = 0{\cdot}72$, $P < 0{\cdot}001$). *Points are fitted with the best-fit linear regression line*

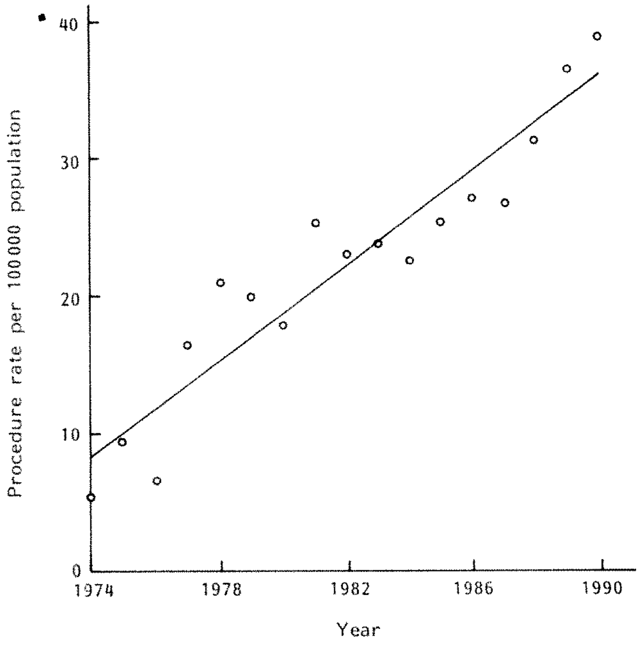

Figure 2 *Arterial reconstruction for lower-limb ischaemia. Data are presented as age- and sex-standardized rates for arterial reconstruction per 100 000 population of Leicestershire* ($r^2 = 0{\cdot}89$, $P < 0{\cdot}001$). *Points are fitted with the best-fit linear regression line*

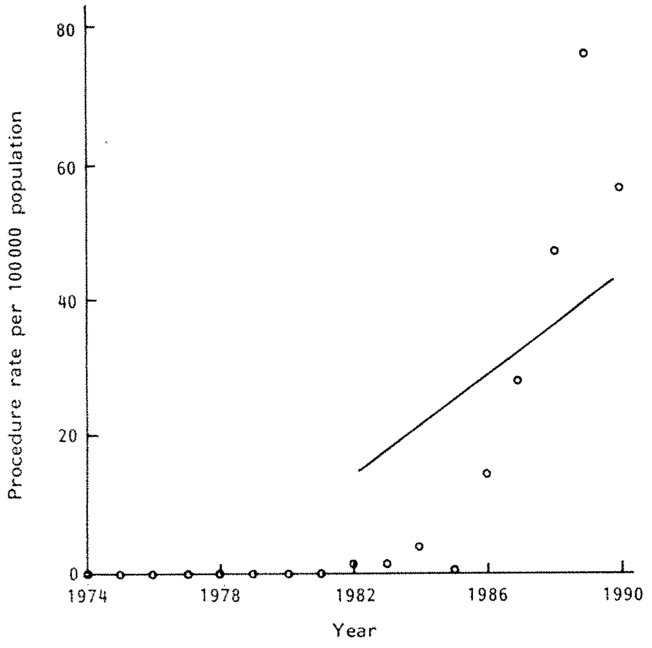

Figure 3 *Percutaneous transluminal angioplasty (PTA) for lower-limb ischaemia. Data are presented as age- and sex-standardized rates for PTA per 100 000 population of Leicestershire ($r^2 = 0.59$, $P < 0.001$). Points are fitted with the best-fit linear regression line*

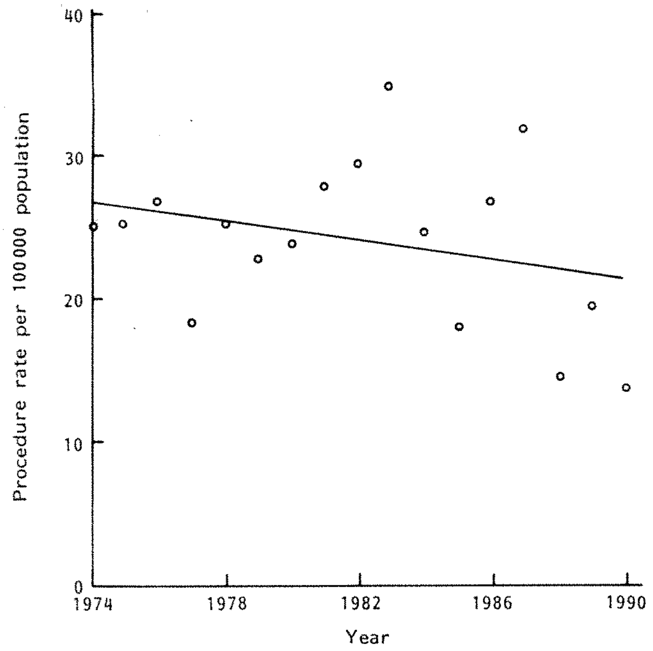

Figure 4 *Major amputation for lower-limb ischaemia. Data are presented as age- and sex-standardized rates for amputation per 100 000 population of Leicestershire ($r^2 = 0.09$, $P = 0.25$). Points are fitted with the best-fit linear regression line*

of reconstructions and PTAs performed before amputation for each year is shown in *Table 4*. Despite the rapid increase in the number of PTAs performed overall, surgical reconstruction remains the preferred treatment option in limb-threatening ischaemia.

Treatment of patients with diabetes mellitus

The methods of treatment of diabetic and non-diabetic patients over the 17-year period are illustrated in *Figure 7*. Overall, 58 per cent of diabetic patients underwent major lower-limb amputation compared with 33 per cent of non-diabetics ($\chi^2 = 143.7$, 1 d.f., $P < 0.001$).

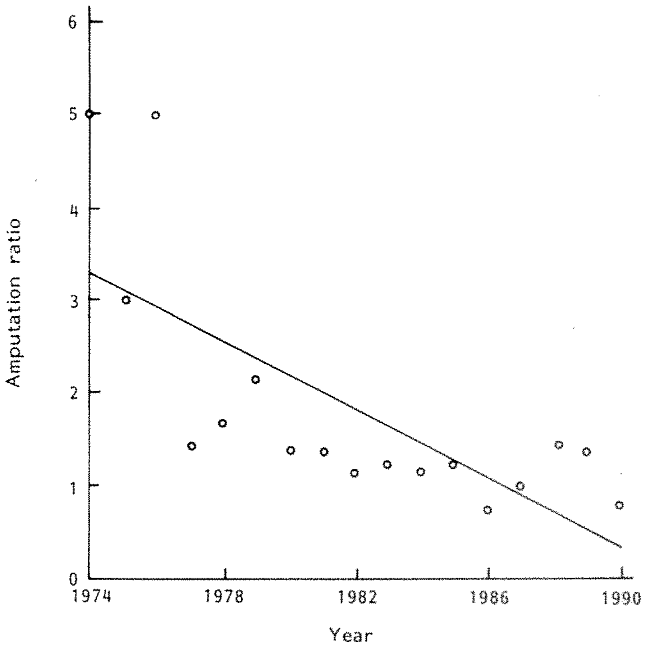

Figure 5 *Change in above- to below-knee amputation ratio over the study period ($r^2 = 0.51$, $P = 0.001$). Points are fitted with the best-fit linear regression line*

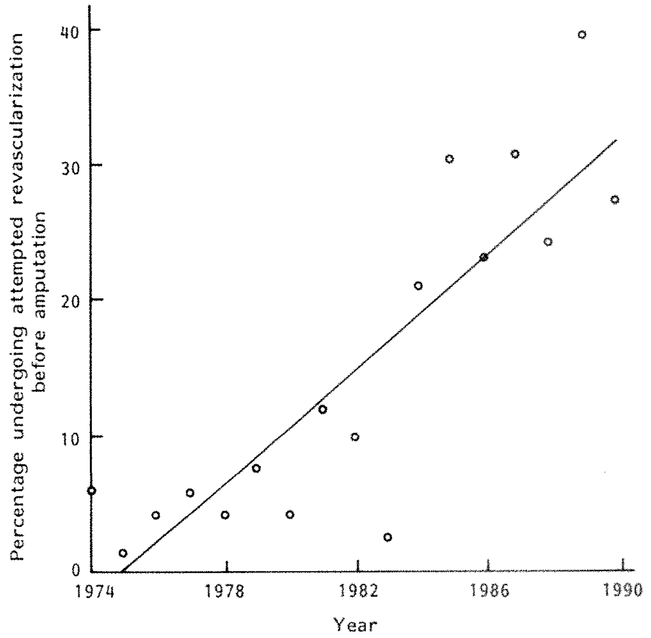

Figure 6 *Percentage of patients per year who underwent attempted revascularization (arterial reconstruction and/or percutaneous transluminal angioplasty) before amputation ($r^2 = 0.75$, $P < 0.001$). Points are fitted with the best-fit linear regression line*

Proportion of elderly patients treated

The percentage of patients over the age of 75 years who underwent either arterial reconstruction, PTA or major lower-limb amputation is shown in *Figure 8*. There was a significant increase in the number of elderly patients who underwent reconstruction or PTA ($r^2 = 0.75$, $P < 0.001$ and $r^2 = 0.58$, $P < 0.001$ respectively). The percentage of patients over the age of 75 years who underwent major amputation also increased during the study period but this increase was not statistically significant ($r^2 = 0.18$, $P = 0.09$).

Duration of hospital stay

The duration of hospital stay for patients undergoing arterial reconstruction or amputation is shown in *Figure 9*. There has

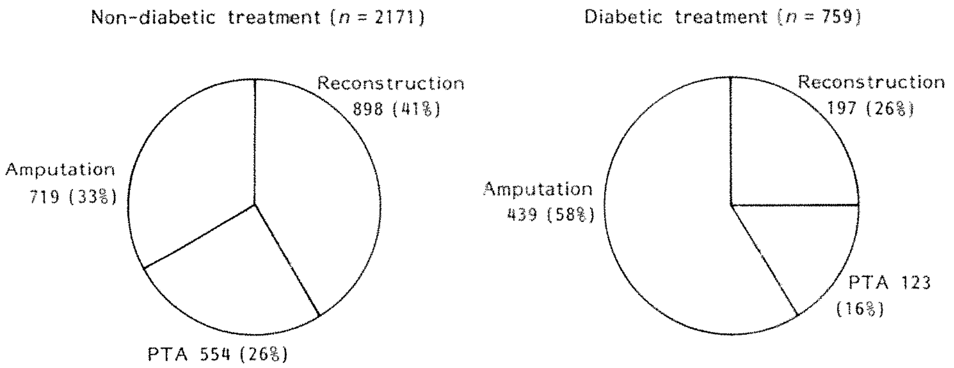

Figure 7 *Treatment of diabetic and non-diabetic patients over the cumulative study period (1974–1990). PTA, percutaneous transluminal angioplasty*

Table 4 *Number of attempted revascularizations, by arterial reconstruction or percutaneous transluminal angioplasty, before amputation*

Year	No. of amputations	Reconstruction	Percutaneous transluminal angioplasty
1974	66	3	0
1975	68	1	0
1976	72	3	0
1977	51	3	0
1978	72	3	0
1979	66	5	0
1980	69	3	0
1981	83	10	0
1982	89	9	0
1983	105	28	0
1984	76	16	0
1985	56	17	0
1986	56	13	0
1987	68	21	0
1988	49	11	1
1989	63	15	10
1990	47	11	2

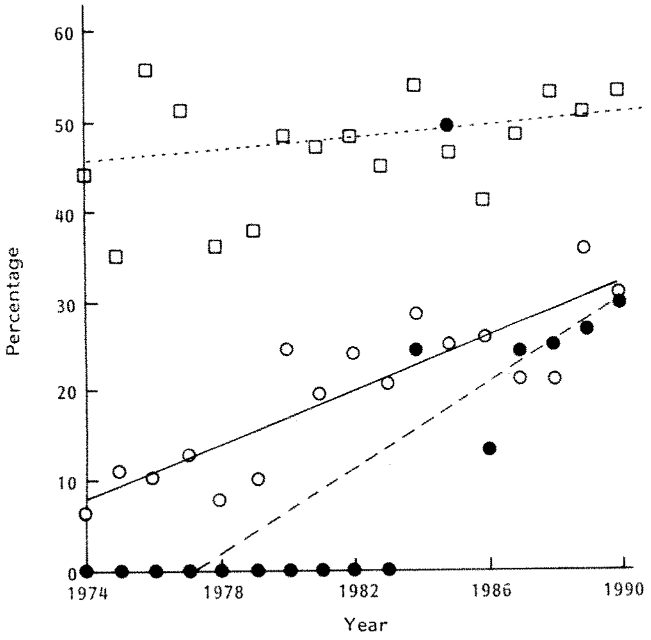

Figure 8 *Percentage of patients over 75 years of age in each of the treatment groups.* ○, *Arterial reconstruction;* ●, *percutaneous transluminal angioplasty;* □, *major lower-limb amputation. Points are fitted with the best-fit linear regression line*

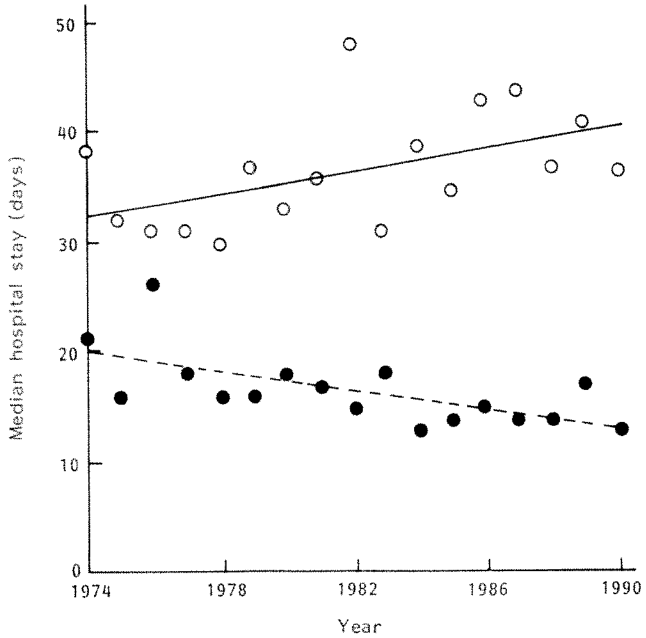

Figure 9 *Median hospital stay of patients undergoing amputation* (○) ($r^2 = 0{\cdot}25$, $P = 0{\cdot}04$) *or reconstruction* (●) ($r^2 = 0{\cdot}42$, $P = 0{\cdot}005$). *Points are fitted with the best-fit linear regression line*

Table 5 *Mortality rate per procedure per year*

	Reconstruction		Percutaneous transluminal angioplasty		Amputation	
Year	Total no.	No. of deaths	Total no.	No. of deaths	Total no.	No. of deaths
1974	15	2 (13)	0	0 (0)	66	13 (20)
1975	27	0 (0)	0	0 (0)	68	19 (28)
1976	19	3 (16)	0	0 (0)	72	11 (15)
1977	47	3 (6)	0	0 (0)	51	7 (14)
1978	60	1 (2)	0	0 (0)	72	9 (12)
1979	58	4 (7)	0	0 (0)	66	16 (24)
1980	52	8 (15)	0	0 (0)	69	19 (28)
1981	75	6 (8)	0	0 (0)	83	24 (29)
1982	69	4 (6)	5	0 (0)	89	15 (17)
1983	71	8 (11)	5	0 (0)	105	31 (30)
1984	69	4 (6)	12	0 (0)	76	20 (26)
1985	78	15 (19)	2	1 (50)	56	14 (25)
1986	56	7 (12)	29	2 (7)	56	11 (20)
1987	55	6 (11)	57	1 (2)	68	18 (26)
1988	98	11 (11)	146	6 (4)	49	16 (33)
1989	119	13 (11)	240	7 (3)	63	20 (32)
1990	127	11 (9)	181	3 (2)	47	8 (17)

Values in parentheses are percentages

been a significant increase in the duration of hospital stay after amputation ($r^2 = 0.25$, $P = 0.04$) and a significant decrease in the duration of hospital stay after reconstruction ($r^2 = 0.42$, $P = 0.005$).

Mortality

The mortality rate expressed as percentage deaths per procedure per year is shown in *Table 5*. Analysis by linear regression revealed that the mortality rate associated with each procedure has not changed significantly during the study period (reconstruction: $r^2 = 0.06$, $P = 0.35$; PTA: $r^2 = 0.06$, $P = 0.33$; amputation: $r^2 = 0.15$, $P = 0.13$).

Discussion

The most significant finding in this study is the dramatic rise in the vascular workload as a result of an increase in the rates of arterial reconstruction and PTA between 1974 and 1990. This in turn is due mainly to expanded indications for intervention in lower-limb ischaemia. It is also likely that advances in other fields of medicine have resulted in more elderly patients presenting with peripheral vascular disease rather than dying from other causes, despite the static prevalence of peripheral vascular disease in the elderly population[3,4]. It is also possible that peripheral vascular disease is being diagnosed more often by clinicians, with subsequent referral of patients for treatment; increasing numbers of repeat procedures are also being performed[5].

The major lower-limb amputation rate has not fallen significantly during the period of this study. Again, this may be because the number of elderly patients presenting with limb-threatening ischaemia is increasing. Although we have no direct evidence of this, there has been a significant increase in the proportion of patients over 75 years old undergoing revascularization. In addition, distal bypass surgery for limb-threatening ischaemia has been performed in Leicester from 1982 onwards[6]; since then, approximately 10 per cent of patients per year undergoing femorodistal bypass have been referred from outside Leicestershire. This commitment to distal vascular reconstruction for critical leg ischaemia[7] is reflected by the increase in the percentage of attempted revascularizations performed before amputation. In this study, there were significantly more amputations in diabetics, which confirms reports from other authors[8,9].

Several previous studies have investigated the effects of modern vascular services on amputation rates and have produced conflicting results. In 1986, Anderson *et al.*[10] found that PTA did not affect the number of reconstructions or amputations performed for peripheral vascular disease, whereas Jeans *et al.*[11] reported that the introduction of PTA was accompanied by an increase in the number of reconstructions and a fall in the number of amputations. In a larger study from the USA, Veith *et al.*[12] demonstrated that an aggressive policy of vascular intervention in the form of PTA and reconstructive surgery was accompanied by a fall in amputation rate. However, all of these studies were from single centres and some contained small numbers or selected subsets of patients; the data were not age- and sex-standardized. In contrast, Tunis *et al.*[5] recently reported an age- and sex-standardized population-based study of 30 000 patients with peripheral vascular disease from Maryland, USA; they found that amputation rates remained static. These findings have been supported by results of other population-based studies[13,14]. Despite the static amputation rate, there has been a significant fall in the ratio of above- to below-knee amputations. This is due to greater awareness that patients undergoing below-knee amputation have a better chance of walking again[15]. There is some evidence now to suggest that failed distal vascular reconstruction does not jeopardize amputation level[16].

There has not been a significant change in the mortality rate associated with arterial reconstruction, PTA or amputation over the period of the present study. It might be expected that the proportionate increase in the number of elderly patients undergoing reconstruction would lead to a higher mortality rate, but this has probably been balanced by advances in anaesthesia and postoperative care. Such advances are also reflected in the decreased duration of hospital stay for patients undergoing arterial reconstruction. Unfortunately, this has been accompanied by an increase in the duration of hospital stay after amputation. The lack of rehabilitation beds locally for amputees may be a major factor in this increase.

In conclusion, there has been a dramatic increase in vascular surgical workload related to the treatment of chronic lower-limb ischaemia over the study period. The increasing demand for vascular surgical procedures has arisen mainly as a result of an increase in the elderly population.

Acknowledgements

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Characterization of symptomatic and asymptomatic carotid plaques using high-resolution real-time ultrasonography

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High-resolution ultrasonography was used to classify carotid plaques into five different types in 72 patients with symptoms and in 49 without, and with stenosis of the origin of the internal carotid artery > 70 per cent. There were 72 plaques in the symptomatic group and 75 in the asymptomatic group. Type 1 plaques were uniformly echolucent, type 2 predominantly echolucent, type 3 predominantly echogenic, type 4 uniformly echogenic and type 5 consisted of plaques that could not be classified owing to heavy calcification and acoustic shadows. Type 1 plaque was found in 90 per cent of patients with symptoms and in 10 per cent of those without, type 2 plaque was found in 53 and 47 per cent, type 3 in 34 and 66 per cent, and type 4 in 5 and 95 per cent, respectively. The preponderance of echolucent plaques in symptomatic patients with stenosis > 70 per cent supports the hypothesis that this type of plaque is unstable and tends to embolize. In contrast, in patients without symptoms there is preponderance of echogenic plaques.

High-resolution B-mode ultrasonography has the major advantage over arteriography that it can be used to characterize atherosclerotic plaques[1]. A classification that allows a closer study of the character and behaviour of plaques was introduced by Steffen *et al.*[2]. Four types of plaque were defined: type 1 is predominantly echolucent, type 2 substantially echolucent with small areas of echogenicity, type 3 predominantly echogenic with small areas of echolucency, and type 4 uniformly echogenic. In symptomatic arteries, irrespective of the degree of stenosis, types 1 and 2 predominate and correlate well with the presence of ulceration and haemorrhage. It has been shown that echolucent plaques have increased lipid and cholesterol levels, which makes them unstable and prone to ulceration and embolization. By contrast, echogenic plaques contain significantly more fibrin and collagen, giving them stability and rendering them less likely to embolize[3,4].

The European Carotid Surgery Trial[5] demonstrated an increased incidence of stroke in patients with transient ischaemic attacks (TIAs) and stenosis >70 per cent who were treated medically, and showed a significant reduction in ipsilateral hemispheric stroke following carotid endarterectomy. It is uncertain whether plaques producing stenosis > 70 per cent are unstable irrespective of echogenicity or whether the findings of Steffen *et al.* hold for this subgroup with severe stenosis.

The aim of this study was to test the hypothesis that, in the presence of stenosis of the internal carotid artery > 70 per cent, the ultrasonographic characteristics of plaques causing symptoms differ from those that do not. It has also been suggested that, with a reduction > 70 per cent in carotid lumen diameter, low flow may cause cerebral infarction or TIA; if this is true, there should be no relation between plaque type and symptoms[6].

Patients and methods

Seventy-two consecutive patients who underwent carotid endarterectomy and 49 who were found to have asymptomatic stenosis by duplex scanning were admitted into the study. The clinical presentation is shown in *Table 1*. All plaques in the symptomatic and asymptomatic groups caused stenosis >70 per cent as confirmed by duplex ultrasonography. In the patients with symptoms only the symptomatic side was assessed; in those without symptoms both sides were assessed. All scans were performed with an Ultramark 4 ATL scanner (Advanced Technology Laboratories, Letchworth, UK) with a 7·5-MHz high-resolution linear scan head. Scan settings (power output 50 per cent, dynamic range 47 dB, gain, gray scale, filters, ramp) were preset at machine start-up and were not altered during the examination. All patients were examined supine with slight head tilt. Anterior, lateral and posterior projections were used to image the plaque longitudinally. All images were recorded on photographic paper. Five types of plaque were defined:

1. Uniformly echolucent plaques. A thin echogenic cap at the margin of the plaque, as previously described by Steffen *et al.*[2], did not have to be visible. Diagnosis of stenosis could be made on the basis of the high-velocity waveform on duplex ultrasonography (*Figure 1*).
2. Predominantly echolucent plaques with <50 per cent echogenic areas (*Figure 2*).
3. Predominantly echogenic plaques with <50 per cent echolucent areas (*Figure 3*).
4. Uniformly echogenic plaques (*Figure 4*).
5. Plaques that could not be classified owing to heavy calcification and acoustic shadows.

Plaques were grouped into one of the above classes by two observers unaware of the presenting symptoms. The between-observer variation in determining the plaque type on the basis of the stated classification

Table 1 *Clinical presentation*

	No. of patients
Patients with symptoms (n = 72)	
Amaurosis fugax	20
Transient ischaemic attacks	31
Stroke	8
Amaurosis fugax plus transient ischaemic attacks	13
Patients without symptoms (n = 49)	
Carotid bruit	28
Peripheral vascular disease	13
Coronary artery bypass surgery	8

Based on a presentation to the Surgical Research Society in Edinburgh, UK, July 1992 and published in abstract form as Br J Surg *1992;* **79**: *1235*

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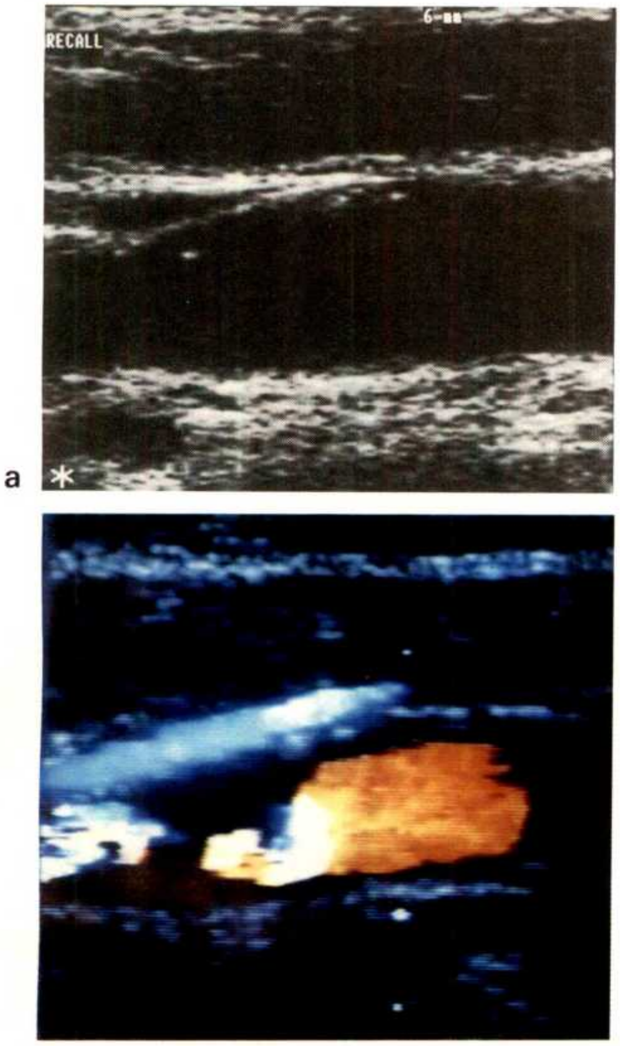

Figure 1 **a** *Ultrasonographic image of uniformly echolucent, 'invisible' (type 1) plaque.* **b** *Addition of colour outlines the margins of the plaque*

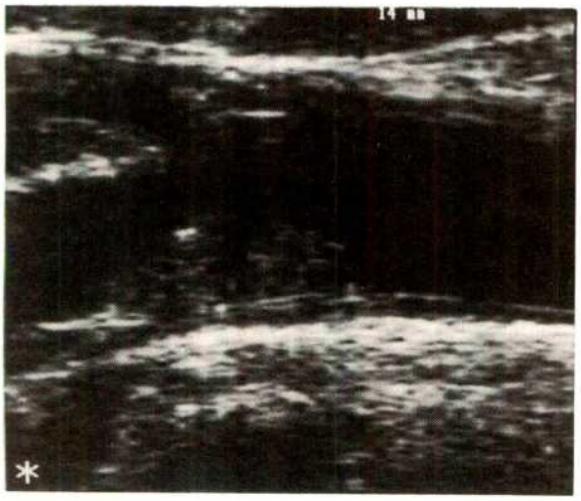

Figure 2 *Ultrasonographic image of predominantly echolucent (type 2) plaque*

was established by randomly selecting 50 patients with 70 carotid plaques. Two observers characterized the plaques from prints, blinded from each other. The κ statistic was used to assess interobserver variation.

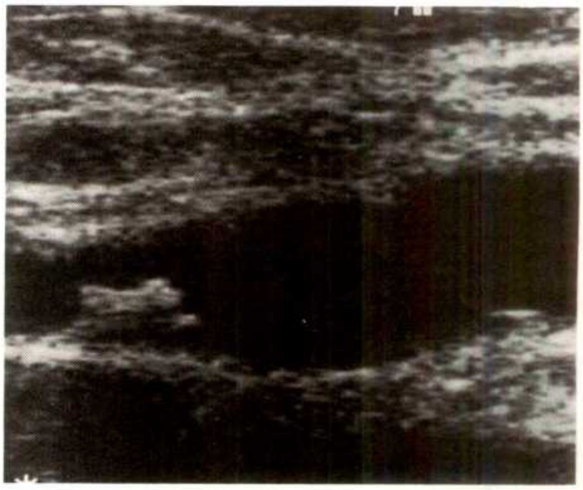

Figure 3 *Ultrasonographic image of predominantly echogenic (type 3) plaque*

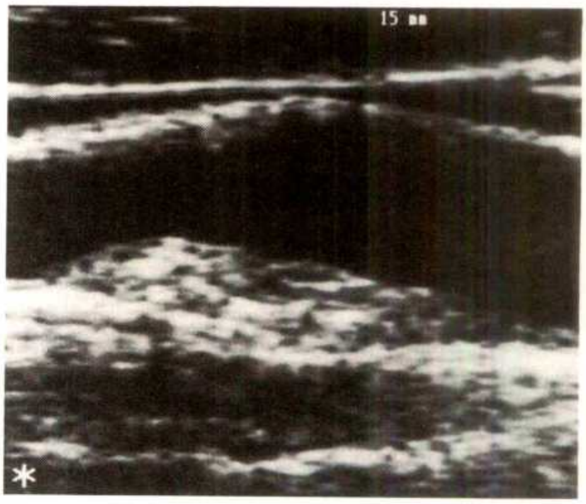

Figure 4 *Ultrasonographic image of uniformly echogenic (type 4) plaque*

Table 2 *Assessment of 70 carotid plaques by two observers*

	First observer					
	Type 1	Type 2	Type 3	Type 4	Type 5	Total
Second observer						
Type 1	20	1	0	0	0	21
Type 2	1	22	1	1	0	25
Type 3	1	4	9	0	0	14
Type 4	0	0	1	7	0	8
Type 5	0	0	0	0	2	2
Total	22	27	11	8	2	70

$\kappa = 0{\cdot}79$

Results

Table 2 shows good agreement on characterization of the carotid plaques into five different types by the two observers ($\kappa = 0{\cdot}79$). The total number of symptomatic plaques in the 72 patients with symptoms was 72 and in the 49 with no symptoms the total number of plaques was 75. Four carotid plaques (two symptomatic, two asymptomatic) could not be classified and were graded as type 5. They were excluded from the final analysis and are not included in *Tables 3* and *4*. The results in *Table 3* show a highly significant association between

Table 3 *Distribution of carotid plaques* of various types according to symptomatic status*

Type	Symptomatic	Asymptomatic
1 ($n = 30$)	27 (90)	3 (10)
2 ($n = 57$)	30 (53)	27 (47)
3 ($n = 35$)	12 (34)	23 (66)
4 ($n = 21$)	1 (5)	20 (95)

Values in parentheses are percentages. *Two symptomatic and two asymptomatic plaques that could not be classified are excluded

Table 4 *Distribution of carotid plaques of various types according to symptomatic status*

	Symptomatic	Asymptomatic
Types 1 and 2	57 (81)	30 (41)
Types 3 and 4	13 (19)	43 (59)
Total	70 (100)	73 (100)

Values in parentheses are percentages. $\chi^2 = 24{\cdot}40$, 1 d.f., $P < 0{\cdot}00001$

the type of plaque and symptoms ($\chi^2 = 39{\cdot}96$, 3 d.f., $P < 0{\cdot}000001$). There was also a highly significant linear trend in proportion to the number of patients with symptoms ($\chi^2 = 38{\cdot}84$, 1 d.f., $P < 0{\cdot}000001$) and no significant departure from a linear trend ($\chi^2 = 1{\cdot}12$, 2 d.f., $P > 0{\cdot}2$). *Tables 3* and *4* summarize the results. There was a predominance of echolucent plaques (types 1 and 2) in the symptomatic group and of echogenic plaques (types 3 and 4) in the asymptomatic group.

Discussion

The European Carotid Surgery Trial[5] has shown that, for symptomatic patients with carotid stenosis of 70–90 per cent, surgery results in a sixfold reduction in ipsilateral stroke. At 3 years after presentation and treatment, the total risk of surgical death, surgical stroke, ipsilateral ischaemic stroke or any other stroke was 12·3 per cent in the group undergoing surgery and 21·9 per cent in medically treated patients. It may be that a subgroup exists among those with stenosis >70 per cent that is at especially high risk of stroke; it may be possible to identify such a group by means of plaque characterization. Conversely, there may be a subgroup at low risk that might also be recognizable using duplex scanning of the plaque.

There is disagreement regarding the correct management of patients with asymptomatic carotid stenosis, and non-invasive imaging techniques have increased the number of asymptomatic lesions diagnosed, creating a dilemma for physicians. Although the overall risk of stroke in patients with asymptomatic stenosis is low, data from five studies suggest that there is a subgroup of patients with no symptoms and stenosis >75 per cent who are at increased risk of stroke[7–11].

Plaque morphology may be a more important factor in the pathogenesis of stroke than the degree of stenosis[12,13]. The composition of plaques from patients with symptoms is significantly different from that of plaques from those without. The former contain more total lipid and cholesterol, and less collagen and calcium[3]. A study correlating pathology with B-mode ultrasonographic imaging has shown that fibrous plaques have a highly echogenic quality. As the lipid content of the plaque increases, the plaque becomes more echolucent[14].

Johnson *et al.*[15] classified asymptomatic plaques according to ultrasonographic characteristics into calcified, dense and soft. At the end of a 3-year follow-up a large proportion of patients with no symptoms and soft plaques had become symptomatic, while only a small proportion of those with calcified plaques developed symptoms[15]. Hennerici *et al.*[16] reported that patients with fibrous carotid plaques who were followed for 18 months had a tendency to remain stable. In contrast, plaque progression was common in those with soft and complex calcified plaques. Spontaneous regression of minor carotid atheroma occurred in soft plaques and corresponded to a reduction in plaque volume. There was a lack of regression in fibrous and calcified plaques[16]. In a recent report from the Committee on Standards in Non-invasive Vascular Testing, it was recommended that plaque characterization should be confined to homogeneous or heterogeneous types[17]. In the present classification, plaque types 1 and 4 were both homogeneous, but homogeneously echolucent lesions were associated with symptoms while homogeneously echogenic plaques were not. The authors are not aware of previous reproducibility studies on carotid plaque characterization, and have shown that there is good inter-observer agreement.

Steffen *et al.*[2] adopted a similar ultrasonographic characterization of carotid artery atheroma and reported that in symptomatic arteries, for all degrees of stenosis, type 1 and 2 lesions were more common (67 per cent), whereas in patients without symptoms the commoner lesions were types 3 and 4 (86 per cent). The present study has confirmed their findings for patients with stenosis >70 per cent. In the light of the above, it is suggested that the present classification might be used in prospective natural history studies of subjects with no symptoms and high-grade stenosis. It might also be used in future studies in which those without symptoms are randomized to operation or medical management. In patients with symptoms and moderate (30–69 per cent) stenosis, the results of the European Carotid Surgery Trial[5] have not shown any benefit of surgery over medical treatment. Perhaps the adoption of plaque characterization would allow recognition of a high-risk subgroup that might benefit from surgery.

Acknowledgements

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Announcement

Inauguration of the Subsection (Division) for Vascular Surgery within the European Union of Medical Specialists

On 6 June 1993 the inaugural meeting took place in Edinburgh, UK, of the subsection for vascular surgery of the monospecialty section for general surgery of the European Union of Medical Specialists (UEMS), an event that marks a small but significant step for the advancement of vascular surgery within the European Community (EC). Establishment of this committee is the first official recognition in Europe of vascular surgery as an entity, albeit one still within the embrace of general surgery, and its purpose is to advise Brussels on matters relating to vascular disease and its treatment within member states.

Each member country has one representative who will serve for 4 years, renewable for a further term. The Chairman and Secretary of the General Surgical Monospecialty Section are *ex officio* members. In addition, the European Society for Vascular Surgery and European Chapter of The International Society for Cardiovascular Surgery may each send a representative to attend meetings but without entitlement to vote. Similar privileges are extended to the Council of Vascular Surgeons.

The constitutional framework within which the subsection will function demands that it is accountable primarily to the management council of the UEMS through the monospecialty section of general surgery. However, it is the intention to disseminate information about its activities to all vascular surgeons in the EC through national representatives.

Matters relating to training will occupy a major part of the proceedings of the subsection. Other topics on the agenda include: preparation of advice on the level of provision of vascular services appropriate for EC countries, promotion of practice guidelines relating to vascular procedures, recommendations on priorities for allocation of research funds, advising on measures to prevent vascular disease, and monitoring vascular surgical activity and standards of practice in member states.

Underlying many of these is the issue of the future of vascular surgery within the Community, whether it is to remain a subspecialty or become a specialty independent of general surgery. The most important consequence of monospecialty status would be the option to establish an independent European Board with the authority to assess candidates and award an EC diploma or certificate of specialist training in vascular surgery. One of the tasks of the subsection will be to gauge the opinion of vascular surgeons in the EC on such issues.

The essential purpose of this new committee is to promote a high standard of clinical practice in vascular surgery throughout the EC. This is an objective with which vascular surgeons of all member countries should be able to identify and towards which it is hoped they will be prepared to lend active support.

P. L. Harris
Chairman
Subsection for Vascular Surgery of the UEMS

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Serial imaging of the carotid bifurcation and cerebrovascular reserve after carotid endarterectomy

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A radioisotopic method of quantifying mean cerebral transit time was used to assess the immediate effects of carotid endarterectomy on cerebrovascular reserve (CVR) in 69 patients. In addition, serial postoperative data were acquired on CVR, clinical status and non-invasive imaging of the internal carotid arteries in 56 patients over a period of 6–48 (median 24) months. Twenty-one patients (30 per cent) had preoperative evidence of impaired CVR in the symptomatic hemisphere. Within 4 days of surgery, however, reserve had returned to normal in 17 of the 21 patients. During follow-up, four of the 56 patients developed recurrent stenosis (>50 per cent) or occlusion of the artery operated on but only two of these had impairment of CVR and none was symptomatic. Three patients suffered recurrent transient ischaemic attacks (TIAs) but none had recurrent internal carotid artery disease or impaired CVR. One patient suffered a TIA in the territory of the non-operated artery during follow-up in association with disease progression and CVR impairment. However, the TIA preceded recognition of either of these changes. Twelve other patients had (or developed) stenosis (>50 per cent) in the non-operated artery during follow-up but none was symptomatic or developed impairment of CVR. Although assessment of CVR provided useful information on the frequency of haemodynamic compromise before carotid endarterectomy and on the natural history of disease progression, neither serial assessment of reserve nor non-invasive imaging of the carotid bifurcation influenced clinical practice during follow-up.

There is considerable variability with regard to the haemodynamic effect of extracranial internal carotid artery stenosis on cerebral blood flow (CBF). Patients with a good collateral circulation maintain normal CBF without recourse to other compensatory mechanisms and have normal cerebrovascular reserve (CVR). If, however, the collateral circulation is poor, the brain is usually still able to maintain CBF by progressive dilatation of the cerebral resistance arterioles, i.e. there is a dynamic state in which CBF is maintained by a simultaneous increase in the cerebral blood volume (CBV). These patients will, however, have some degree of impairment of CVR: they have a reduced capacity to undergo further compensatory vasodilatation.

The concept of impaired CVR is of considerable current interest. Preliminary studies[1–4] suggest that patients with impaired reserve may be more likely to suffer a stroke or neurological deficit during carotid endarterectomy than those with normal CVR, possibly because the former are more susceptible to minor embolic phenomena or low-flow states. It might be speculated that early recognition of impairment of CVR could identify patients at risk of developing recurrent symptoms following carotid endarterectomy.

The aim of this study was to evaluate the immediate and long-term effects of carotid endarterectomy on CVR, and to correlate patterns of restenosis and disease progression during follow-up with the development of impairment of CVR and clinical outcome.

Patients and methods

Seventy-one consecutive patients undergoing carotid endarterectomy at Edinburgh Royal Infirmary were included in the study. Two who suffered major perioperative strokes and who did not undergo postoperative assessment were excluded from further analysis. Permission for the study was obtained from the Lothian Area Surgical Ethics Committee and the UK Administration of Radioactive Substances Advisory Committee, and patients were entered after obtaining their informed consent.

Preoperative assessment

All patients underwent carotid angiography, computed tomography (CT) and an evaluation of CVR. The degree of stenosis in the internal carotid artery was determined as the maximal biplane diameter reduction as a percentage of the normal diameter of the artery above the stenosis[5].

The principle underlying assessment of CVR is that, as the pial vessels undergo compensatory vasodilatation, there is a simultaneous increase in CBV. Accordingly, impairment of reserve can be recognized by: (1) testing the residual capacity of arterioles to undergo further dilatation in response to hypercapnia[5,6]; or (2) generating, after measurement of basal CBF and CBV, a final image that displays the ratio of CBF to CBV. Studies[7] using positron emission tomography (PET) suggest that the ratio of CBF to CBV is one of the most sensitive indicators of impairment of reserve. According to the basic flow equation (flow = volume/time), this ratio is an expression of the reciprocal of mean cerebral transit time (MCTT), i.e. any compensatory increase in CBV will cause a simultaneous increase in MCTT. This fact was acknowledged by Gibbs *et al.*[7], who recognized that quantification of MCTT could provide a simpler alternative to PET for studying CVR.

A method has been developed for quantifying regional and hemispheric MCTT following an intravenous injection of ^{99m}sodium pertechnetate[8,9]. After correction for the error due to bolus dispersion[8], the technique generates a parametric image of cerebral transit time (*Figure 1*) in which each colour represents an increment of 0·5 s in time (range 0–15 s). Although regional variations in transit time can be determined from the colour scale, the computer determines the mean transit time for each hemisphere and also the interhemispheric difference

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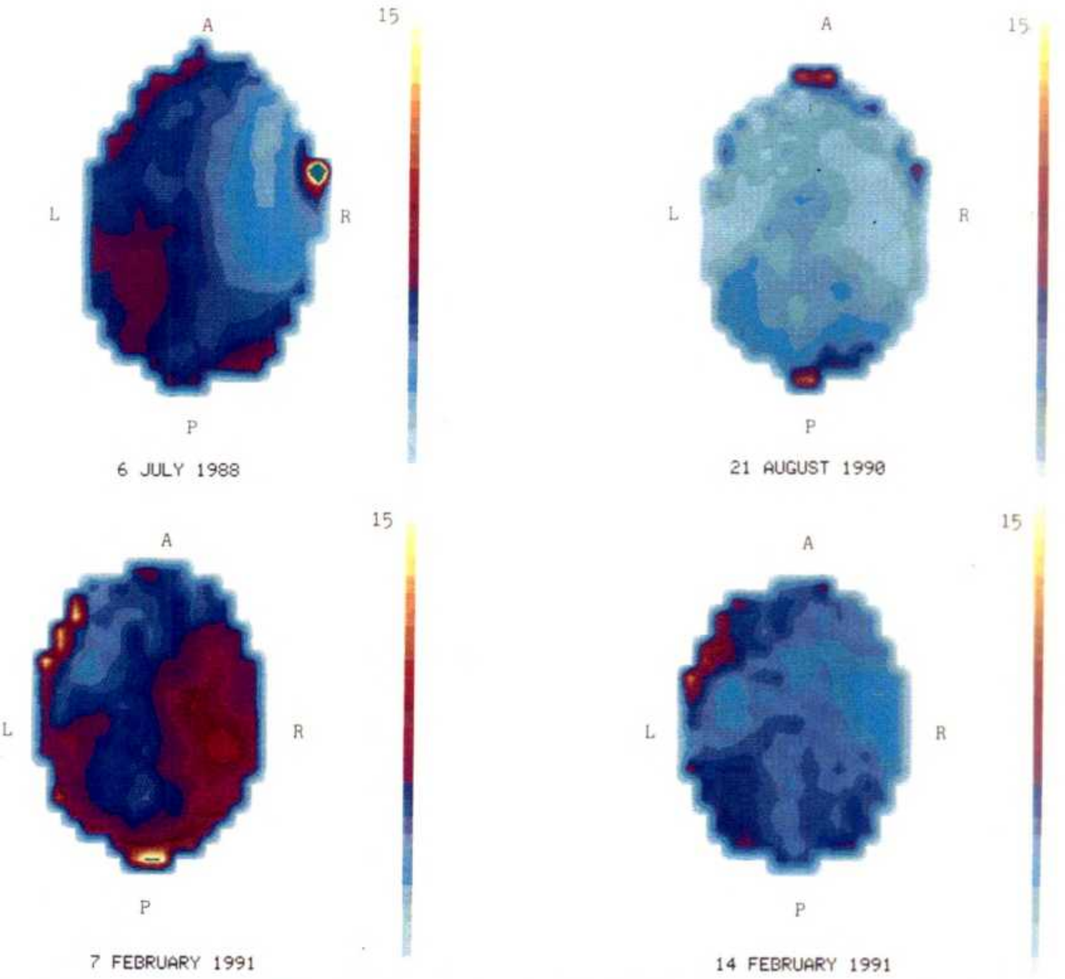

Figure 1 *Serial mean cerebral transit time (MCTT) studies in one patient over 29 months following carotid endarterectomy.* **a** *Initial preoperative study in a patient with 90 per cent stenosis of the left internal carotid artery. Note the loss of normal interhemispheric MCTT symmetry with prolongation of transit time throughout the left hemisphere.* **b** *MCTT study 2 years after left carotid endarterectomy when duplex ultrasonography suggested 50 per cent stenosis of the right internal carotid artery; cerebrovascular reserve (CVR) is normal.* **c** *At 29 months after left carotid endarterectomy, the patient presented with a transient ischaemic attack in the right carotid territory and now has 90 per cent stenosis of the right internal carotid artery. Note the presence of impaired CVR throughout the right hemisphere.* **d** *At 4 days after right carotid endarterectomy; CVR is now normal bilaterally. A, anterior; P, posterior; L, left hemisphere; R, right hemisphere, i.e. one is looking down on the skull vertex. Each colour represents an increment of 0·5 s in MCTT (range 0–15 s)*

in MCTT. *Figure 1b* shows a normal study. The normal pattern is one of shorter MCTTs at the front of the brain with longer transit times posteriorly but, most importantly, close symmetry in transit time is maintained between hemispheres.

In comparative studies with transcranial Doppler ultrasonography (no PET scanner is available to the authors), it has been shown[9] that hypercapnia causes a significant and symmetrical reduction in hemispheric MCTT, and a symmetrical and bilateral increase in blood flow velocity in the middle cerebral artery. In addition, blood flow velocity changes in direct proportion to the reciprocal of hemispheric MCTT, i.e. the CVR[9].

The normal range of mean hemispheric transit time (2·2–7·7 s) reflects the wide range of interindividual variability that is typical of all methods used to measure the parameters of cerebral circulation. Interhemispheric MCTT symmetry is, however, closely maintained throughout the physiological range of end-tidal carbon dioxide levels (upper 95 per cent confidence limit for interhemispheric MCTT difference[8,9] 0·6 s). In the present study, specific use was made only of those values of hemispheric MCTT and interhemispheric asymmetry that had been determined by the system computer, i.e. impaired CVR was not diagnosed on the basis of visual interpretation of the image. Accordingly, impaired reserve was defined as a hemispheric MCTT $>7{\cdot}7$ s or significant interhemispheric transit time asymmetry $\geqslant 0{\cdot}7$ s.

Figure 1a shows a typical example of impaired CVR in a patient with 90 per cent stenosis of the left internal carotid artery (no significant disease in the contralateral artery). Note the loss of normal interhemispheric MCTT symmetry with prolongation of transit times throughout the territory of the left artery.

Operative technique

Carotid endarterectomy was performed under normotensive normocarbic general anaesthesia with systemic heparinization. The nerve to the carotid sinus was not anaesthetized or divided in any patient and all but one arteriotomy was closed with a vein patch. Patients had carotid shunts inserted using the criterion of slowing of the cerebral function monitor or an internal carotid artery stump pressure <50 mmHg. Five patients recovered from anaesthesia with a transient minor intraoperative neurological deficit, three of which represented slight worsening of a pre-existing deficit. The deficit resolved within days in all but two patients, who still had some residual weakness of the hand at 7 days. All patients received aspirin after operation, unless contraindicated.

Postoperative assessment

MCTT studies were repeated on day 4. All patients suffering an intraoperative neurological deficit underwent re-exploration, intravenous digital subtraction angiography (DSA) or duplex ultrasonography of the operated internal carotid artery. Fifty-six patients were then serially evaluated over 6–48 (median 24) months, with repeated assessment of clinical status and CVR, and non-invasive imaging of the carotid bifurcation (initially by intravenous DSA, latterly by duplex ultrasonography and Doppler waveform analysis) every 6 months for the first year and annually thereafter. Endpoints of the study were the development of cerebrovascular symptoms, impaired CVR, or the presence of internal carotid artery stenosis >50 per cent or occlusion. In two patients, serial imaging of the CVR was abandoned after 24 months because of poor cardiac output. Thirteen patients did not undergo serial postoperative assessment. Twelve had not reached their first 6-month follow-up by completion of the study, and one was found to have metastatic prostatic carcinoma within months of operation and was unfit for review.

Results

Forty-six patients presented with transient ischaemic attack (TIA) or amaurosis fugax, 20 with stroke (16 with residual deficit), and three with central retinal artery occlusion; 56 had a symptomatic stenosis >50 per cent. Fifty-eight patients had either no disease or stenosis $\leqslant 50$ per cent in the non-operated artery, seven a contralateral artery stenosis >50 per cent and four a contralateral carotid occlusion. Nineteen patients had a hypodense area in the symptomatic hemisphere on CT, consistent with an area of old infarction, while nine had infarction in the non-operated hemisphere.

Immediate effect of carotid endarterectomy on cerebrovascular reserve

Twenty-one patients (30 per cent) had preoperative evidence of impaired CVR in the symptomatic hemisphere and all had internal carotid artery stenosis >60 per cent. None of the seven patients with a contralateral artery stenosis >50 per cent had evidence of impaired vascular reserve, but three of the four with a contralateral occlusion had an impaired reserve in the non-operated hemisphere. One of the latter had bilateral impairment of CVR.

Of the 21 patients with impaired reserve in the symptomatic hemisphere, the CVR returned to normal in 17 within 4 days of operation. In only one of the remaining four patients had the CVR not returned to normal by 6 months. Four patients had a normal preoperative CVR study but then developed significant abnormality after operation. In two patients MCTTs in the symptomatic hemisphere were very short and probably represented transient postoperative hyperaemia. Two, however, developed impaired CVR in the symptomatic hemisphere. Because of the unexpected nature of these findings intravenous DSA was undertaken, which showed in both that the operated internal carotid artery had occluded without symptoms.

Long-term effect of carotid endarterectomy on cerebrovascular reserve

The hemisphere operated on (Table 1). Fifty-one of the 56 patients had no evidence of either recurrent disease in the operated internal carotid artery or impaired CVR during follow-up. Three patients suffered TIAs at 14, 15 and 23 months respectively; none had an obvious cardioembolic source but one had stenosis of the ipsilateral external carotid artery.

Two patients had impaired reserve in the operated hemisphere at 6 months and both had suffered asymptomatic occlusion of the operated artery (verified angiographically). The first was discussed earlier, having been noted to have unexpected impairment of vascular reserve after operation. The second initially presented with impaired CVR and then suffered an intraoperative neurological deficit. Re-exploration found no abnormality of the segment operated on. The first postoperative MCTT study, however, remained abnormal and it may be that by this time the internal carotid artery had occluded asymptomatically. Interestingly, serial CVR studies in these two patients showed progressive improvement, and by 12 months both had returned to normal and remained so when rechecked at 24 months.

Table 1 *Long-term outcome for the operated artery in 56 patients*

	Impaired CVR	Normal CVR
Recurrent disease (>50% stenosis or occlusion)	2*	2†
No recurrent disease	1	51‡

CVR, cerebrovascular reserve. *Occlusion of both internal carotid arteries; impaired CVR had returned to normal 12 months after surgery; †60 per cent stenosis at 24 months, 75 per cent at 36 months; ‡three patients had recurrent transient ischaemic attacks

Two patients developed significant restenosis in the operated internal carotid artery during follow-up; neither stenosis was symptomatic or associated with impaired CVR. The remaining patient had no evidence of recurrent carotid disease but had persistently impaired vascular reserve in the operated hemisphere (up until last review at 3 years). This patient had had preoperative evidence of impaired reserve as well as a residual neurological deficit (which worsened transiently during operation); perhaps more importantly, he had preoperative CT evidence of three cortical infarcts in the territory of the symptomatic middle cerebral artery. This may explain why the abnormality in CVR did not resolve after operation.

The non-operated hemisphere (Table 2). Forty of the 56 patients remained asymptomatic throughout follow-up with no evidence of either disease progression or impairment of CVR. Twelve patients had internal carotid artery stenosis >50 per cent but normal vascular reserve; in five this represented no change from the preoperative findings while in seven there was evidence of significant disease progression. None of the twelve developed any clinical symptoms, apart from one hypertensive patient who suffered a fatal haemorrhage in the non-operated hemisphere at 24 months.

The most interesting subgroup were the four patients with significant contralateral carotid disease and evidence of impaired CVR. Three were known before operation to have occlusion of the internal carotid artery. Although surgery did not appear to alter the overall degree of interhemispheric MCTT asymmetry, regional transit times were generally reduced throughout both hemispheres, suggesting at least partial improvement in CVR. The serial MCTT studies in the fourth patient in this group are shown in *Figure 1*. She presented with 90 per cent stenosis of the left internal carotid artery and only minor irregularity of the right artery on ultrasonography and angiography (*Figure 2a*). Her preoperative transit time study (*Figure 1a*) showed evidence of impaired CVR in the symptomatic left hemisphere (interhemispheric MCTT difference 2·0 s). After operation the transit study results returned to normal, with restoration of symmetry (interhemispheric MCTT difference 0·3 s). Ultrasonography (duplex plus Doppler ultrasonographic waveform analysis) at 6 and 12 months showed no significant stenosis at either bifurcation, and transit time study results remained normal. At 2 years after operation, while the patient was still asymptomatic, ultrasonography suggested that stenosis in the non-operated artery had progressed to about 50 per cent but there was still no corresponding abnormality in vascular reserve (*Figure 1b*). However, 6 months later she presented with a TIA. By this

Table 2 *Long-term outcome for the non-operated artery in 56 patients*

	Impaired CVR	Normal CVR
Stenosis >50% or occlusion		
Disease static	0	5
Preoperative occlusion of internal carotid artery	3	0
Disease progression	1*	7†
Total	4	12
Normal or stenosis $\leqslant 50$%	0	40

CVR, cerebrovascular reserve. *Stenosis increased from 10 to 90 per cent over 30 months; patient suffered a transient ischaemic attack at 29 months. †Stenosis increased in two patients from 50 to 75 per cent and from 50 to 80 per cent over 12 months, in three from 40 to 60 per cent, from 75 to 90 per cent and from 30 to 80 per cent over 24 months, and in two from 30 to 60 per cent and from 0 to 70 per cent over 36 months

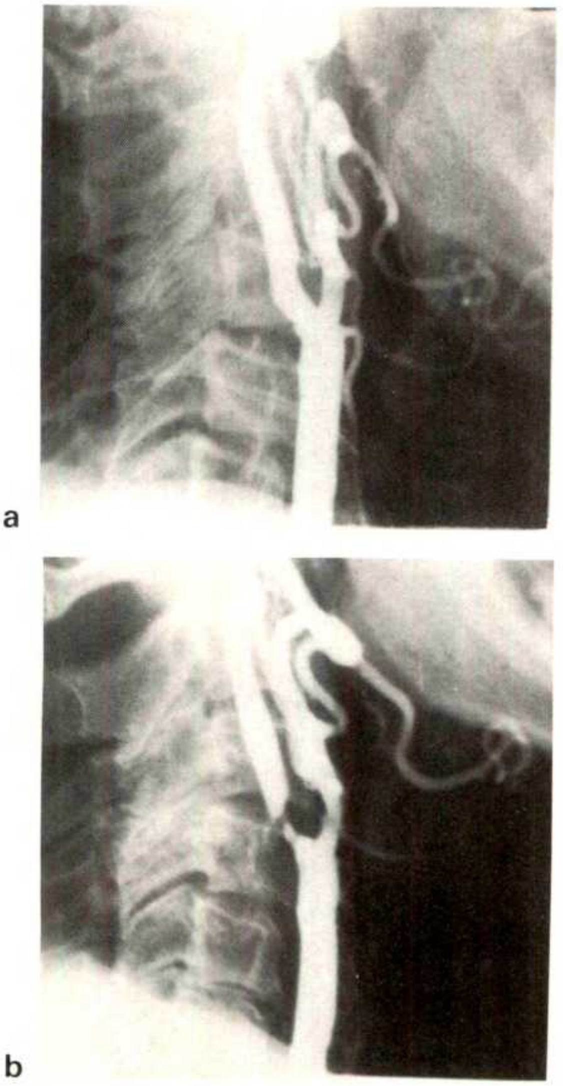

Figure 2 *Angiography of disease progression in the non-operated carotid bifurcation of the patient described in* Figure 1. **a** *Minimal irregularity at the time of first carotid endarterectomy;* **b** *severe stenosis 29 months after the original carotid surgery when the patient presented with a transient ischaemic attack*

time ultrasonography, and subsequently angiography, revealed a very tight stenosis (*Figure 2b*). When the transit time study was repeated (*Figure 1c*) there was clear evidence of impaired vascular reserve throughout the right hemisphere (inter-hemispheric MCTT difference 1·7 s). At operation, the plaque was found to have ruptured, with overlying thrombus and loose atheromatous debris. After operation CVR study results again returned to normal (*Figure 1d*).

Discussion

Evaluation of the haemodynamic state of the cerebral circulation must take into account the dynamic changes that occur in the ratio of CBF to CBV. This awareness has led to the development of a number of methods designed to assess the capacity of the cerebral circulation to undergo further vasodilatation. None, however, specifically tests the individual contributions of the carotid and vertebrobasilar inflows but rather the capacity to respond of the cerebral circulation as a whole. The most common of these methods is the response to hypercapnia or following administration of acetazolamide, although carbon dioxide reactivity is a partially independent mechanism to autoregulatory vasodilatation in response to a declining cerebral perfusion pressure[10]. Using a hypercapnic stimulus, CVR has been evaluated using conventional ^{133}xenon washout methods[5], single photon emission computed tomography[11], transcranial Doppler ultrasonography[6] and PET[7,12]. Stress tests, however, require two separate studies, patient compliance and (in the case of the tomographic methods) minimal head movement during data acquisition. Moreover, tomographic equipment is not widely available to clinicians in the UK and doubt has been cast[13] on the validity of some of the agents used to measure carbon dioxide reactivity.

The transit time method is one of several means of studying CVR with the virtues of speed, simplicity, availability and low cost. However, it is limited by the lack of anatomical precision offered by tomographic methods; it cannot individually quantify either CBF or CBV; and it requires a good cardiac output. Poor cardiac output is the principal reason for poor diagnostic imaging. Its application is based on a sound theoretical basis derived from PET studies[7] and it has been proposed[14] that changes in MCTT should parallel changes in perfusion pressure. While unable to demonstrate a relationship between the oxygen extraction fraction and either CBF or CBV, Gibbs and colleagues[7] found a clear relationship between oxygen extraction fraction and the ratio of CBF to CBV. As the stenosis becomes more significant haemodynamically, CBV increases to maintain CBF. The corresponding increase in MCTT probably occurs at capillary and precapillary levels, and permits an increase in the oxygen extraction fraction by virtue of the increased surface area and time available for diffusion[15]. Moreover, it has been shown that once the ratio of CBF to CBV is $<5{\cdot}5$ (equivalent to a hemispheric MCTT[8] >11 s), there is always an increase in the oxygen extraction fraction. This implies that the lower limits of autoregulation and perfusion reserve have been reached[7,16]. Such an extreme situation was encountered in only one of the present patients with bilateral impaired CVR (symptomatic hemisphere MCTT 9·4 s, asymptomatic hemisphere MCTT 11·8 s) and bilateral carotid disease (90 per cent stenosis and contralateral occlusion respectively).

In the present study, carotid endarterectomy restored normal CVR in 81 per cent of patients with preoperative abnormalities; this is in line with the experience of others[17–19]. However, the effect of carotid surgery on CBF and CVR is influenced by patient selection. The main haemodynamic effect of carotid endarterectomy is an increased flow in the internal carotid artery and a redistribution of cerebral perfusion as the need for collateral flow is reduced[20]. In a comprehensive review, Schroeder and Jones[3] found that patients with carotid stenosis <50 per cent had no significant increase in CBF after operation, while those with stenosis >50 per cent had a variable response but tended to show an increase in CBF. The most marked increases in postoperative CBF were in patients with stenosis >80 per cent, i.e. those most likely to have impaired CVR.

The present study has also shown that the restoration of normal CVR is generally maintained throughout follow-up and correlates well with non-invasive imaging of the carotid bifurcation. Little emphasis should be placed on transient early asymmetries that might be due to postoperative hyperaemia, as these have almost invariably disappeared[5] by 6 months. However, the unexpected finding of residual (or new) impairment of CVR in the symptomatic hemisphere should raise the possibility of an asymptomatic carotid occlusion. Moreover, the present study has demonstrated that, with time, any impairment in CVR associated with carotid occlusion might return to normal as the collateral circulation develops.

Although the authors' policy of assessment of CVR and non-invasive imaging of the endarterectomy site has provided useful information on the durability of carotid endarterectomy and the rather unpredictable nature and sequeliae of disease progression, it has not led to any changes in clinical practice. The hypothesis that recurrent symptoms might be anticipated by preceding changes in CVR has not been borne out; none of the patients with recurrent symptoms in the territory of the operated internal carotid artery had either significant recurrent disease or CVR abnormality. Similarly, while 13 patients under follow-up had significant stenosis in the non-operated artery (five static, eight as a consequence of disease progression), only one developed symptoms. Although the TIA in this patient was associated with the development of impaired CVR, she had already presented clinically before evidence was forthcoming of the rapid disease progression and haemodynamic impairment. Because of the findings at operation, it is presumed that this patient's symptoms and disease progression were attributable to plaque rupture; there was nothing in the preceding 2 years of follow-up to differentiate her from the other seven patients with disease progression. In agreement with other authors, therefore, no compelling clinical or cost-effective indication has been found for continuing with serial assessment of either CVR or the carotid bifurcation beyond the early postoperative period. Such investigations should be reserved for the very few patients who develop secondary symptoms.

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Surgical workshop

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Cryostripping the long and short saphenous veins

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Conventional stripping of the long or short saphenous vein requires two incisions. The purpose of the distal incision is to tie the vein to the stripper so that the two may be withdrawn together. Cryocoagulation avoids this requirement.

Surgical technique

After flush saphenofemoral disconnection in the groin, the trunk of the long saphenous vein (LSV) is emptied by limb elevation and catheterized with a probe connected to a liquid nitrogen cryosurgery unit (Erbe, Tubingen, Germany). When the probe has reached the upper calf, its tip is chilled to −80°C; cryocoagulation occurs within about 5 s. With the tip kept frozen, the probe is then steadily withdrawn while an assistant compresses the LSV below the site of coagulation. This causes disruption of the vein, which is then stripped upwards to the groin (*Figures 1* and *2*). Tributaries are avulsed *en route*. Since there is no distal incision, it is necessary to measure the length of retrieved vein to ensure that stripping is complete. It is important not to keep the frozen tip of the probe at one position in the leg for more than about 10 s, as this risks damage to extraluminal structures, especially the saphenous nerve. Our impression is that the technique entails less blood loss than conventional stripping, although this has not been quantified.

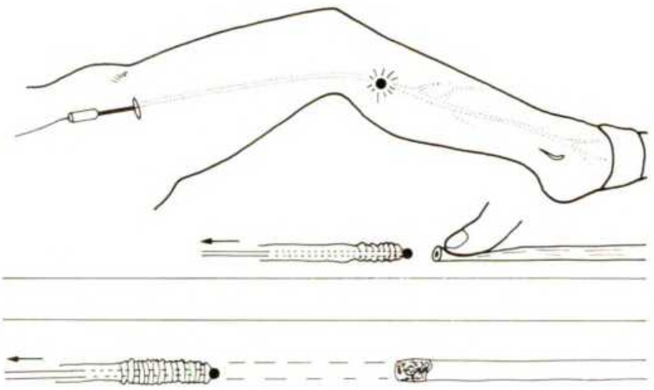

Figure 1 *Diagrammatic representation of cryostripping*

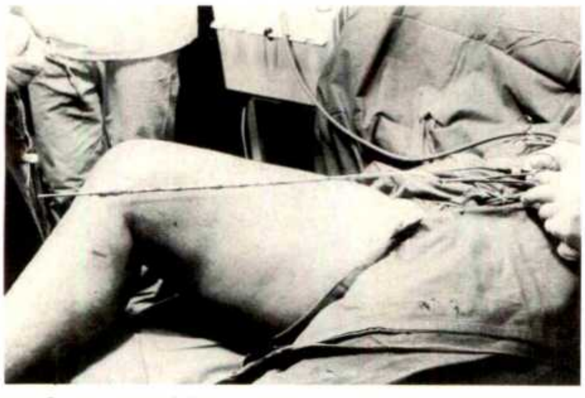

Figure 2 *A stripped long saphenous vein after withdrawal of the cryoprobe. A pen mark below the patient's knee indicates the point at which stripping was started*

Discussion

Between 1 January and 30 June 1992 one surgeon (M.P.) stripped 386 LSVs and 75 short saphenous veins (SSVs). Cryostripping was used in 105 (27 per cent) and 16 (21 per cent) cases respectively. The authors' indications for cryostripping are:

1. When multiple distal avulsions of varicosities are not being performed, and where the cosmetic benefit of avoiding a distal incision is therefore maximized. The majority of such patients had had sclerotherapy to control varicosities.
2. When one or more large tributaries of the LSV in the groin, such as the anteromedial or posterolateral superficial veins of the thigh, needs to be stripped in addition to the LSV itself. These veins can all be stripped upwards through a single groin dissection.
3. When liposclerotic skin in the calf makes a distal incision hazardous. This especially applies to the SSV.

In an attempt to identify complications, 100 patients who had undergone cryostripping were sent a postal questionnaire in which they were asked about adverse postoperative events. Sixty-one responded, of whom 11 (18 per cent) said they had suffered complications. These comprised two patients with superficial thrombophlebitis, seven in whom a numb patch of skin occurred, one with oedema and one with nervous depression. The nine instances of thrombophlebitis or hypoaesthesia were all transient and have resolved completely. The authors are aware of one case early in their experience where the saphenous nerve was permanently damaged, probably by prolonged freezing at the site of vein disruption.

Since the concept of cryostripping was first introduced by Milleret[1], the technique has become an established part of the authors' armamentarium. It is simple, inexpensive and slightly quicker than conventional stripping since no distal incision, dissection or closure is required. It is recommended to all surgeons performing regular saphenous stripping.

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Suture length to wound length ratio and healing of midline laparotomy incisions

The effect of suture length to wound length ratio on the healing of midline laparotomy wounds closed with a continuous suture was evaluated in a prospective clinical trial. All patients undergoing abdominal procedures through a midline incision were included except those with an incisional hernia after previous midline operation. The total incidence of wound infection was 36 of 454 patients (7·9 per cent) and wound dehiscence requiring reoperation occurred in three patients (0·7 per cent). Incisional hernia was found in 18·7 per cent of 363 patients alive 12 months after surgery. Multivariate analysis identified the suture length to wound length ratio, age and major wound infection as independent risk factors for the development of hernia, which occurred in 9·0 per cent of patients when the suture length to wound length ratio was ≥4 and in 23·7 per cent ($P = 0{\cdot}001$) when it was <4. The suture length to wound length ratio is an important parameter for healing of midline incisions closed with a continuous suture technique. The incidence of incisional hernia is lower when such wounds are sutured with a ratio ≥4.

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Closure of midline laparotomy incisions with a single layer of continuous monofilament suture is a well established method[1-8]. Trials have compared interrupted and continuous suture techniques and found the latter to be more rapid, whereas the safety of the two methods appears to be similar[9-12].

Experimental evidence suggests that continuous suturing gives the best results when the suture length to wound length ratio is 4:1, i.e. the length of suture material consumed is four times the length of the wound[1,6,13-15]. An optimal suture length to wound length ratio has yet to be determined in a clinical trial. This prospective study assessed how this ratio affects early and late healing of midline laparotomy wounds.

Patients and methods

A prospective trial was started in August 1989 in which all surgeons, including residents in training, participated. All patients undergoing abdominal surgery through a midline incision were eligible for the trial; only those with an incisional hernia after previous midline surgery were excluded. Patients were stratified according to age, sex, previous midline laparotomy, urgency of operation and degree of operative contamination[16,17].

The fascia was sutured with a continuous single-layer mass-closure technique including all layers except skin. The surgeon was free to choose whether peritoneum was included in the suture or not. The starting knot was a modification of the half blood-knot, and the suture was ended with a chain stitch knot[18-21]. For reasons not relevant to the present study, patients were randomized to closure with polydioxanone or nylon, no. 1, delivered in lengths of 150 cm (*Figure 1; Table 1*). The length of the incision was measured after closure of the fascia and the length of suture consumed (150 cm − length of suture remnants) measured for calculation of the suture length to wound length ratio.

Early wound complications were recorded. Infection was defined as purulent discharge from the wound; bacteriological cultures were not mandatory. Wound infection was classified as minor or major. Major wound infection was accompanied by general symptoms and an increased length of hospital stay[16,22].

Patients alive 12 months after surgery were examined for the presence of incisional hernia. This was defined as a palpable defect in the fascia, or a protrusion beyond the level of the fascia with the patient examined supine lifting both legs and coughing or straining in an erect position. Examinations were carried out by the same surgeon (L.A.I.) except when patients had moved from the area, when they were examined by a local physician.

Univariate statistical analysis used the χ^2 test with Yates' correction or Fisher's exact test as appropriate. Factors identified as significant on univariate analysis were subjected to multivariate analysis using multiple linear regression. Differences were regarded as significant at $P < 0{\cdot}05$.

Results

From August 1989 to March 1991, 454 patients were entered into the trial. The length of the laparotomy incision ranged from 10 to 86 (mean 27) cm. The mean suture length to wound length ratio was 3·6.

Early results

Minor and major wound infection each occurred in 4·0 per cent of patients. The suture length to wound length ratio did not affect the incidence of infection. Wound dehiscence requiring resuture occurred in three patients (0·7 per cent). In one of these, suture and wound lengths were not registered, but closure in the other two patients was with a suture length to wound length ratio of 1·25.

Late results

Eighty-six patients died within 12 months of surgery, three were excluded from late follow-up because of early wound dehiscence and two were ineligible because of violation of the study protocol. The remaining 363 patients were all available for follow-up examination. The overall incidence of incisional hernia 12 months after surgery was 18·7 per cent. The incidence of hernia was related to the suture length to wound length ratio. When the ratio was <4, hernia occurred in 23·7 per cent of patients (57 of 241), whereas the incidence was 9·0 per cent (11 of 122) if the ratio was ≥4 ($P = 0{\cdot}001$; *Table 2*). The two groups of patients were comparable with regard to all variables recorded (*Table 1*). The association between suture length to wound length ratio and hernia was similar for both suture materials used (*Figure 1*).

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On univariate analysis, sex, previous midline laparotomy, emergency operation and minor wound infection were not related to the subsequent development of hernia whereas age, length of incision and major wound infection were significantly correlated. Hernia was found in 62 of 279 patients (22·2 per cent) older than 45 years compared with six of 84 (7 per cent) aged 45 years or younger ($P < 0{\cdot}01$; *Figure 2*). The hernia rate was 25·2 per cent (33 of 131) when incisions were longer than 27 cm and 15·1 per cent (35 of 232) for those of 27 cm or shorter ($P = 0{\cdot}03$). The incidence of hernia was six of 14 patients with major wound infection compared with 58 of 332 when there was no infection ($P = 0{\cdot}04$). The suture length to wound length ratio affected the hernia rate even in the presence of major wound infection; hernia occurred in six of eight of these patients when the ratio was <4 but in none of six when it was ≥4 ($P < 0{\cdot}01$).

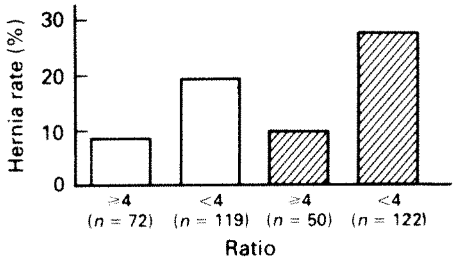

Figure 1 *Incidence of incisional hernia 12 months after operation in relation to suture length to wound length ratio for wounds sutured with polydioxanone* (□) *and nylon* (▨)

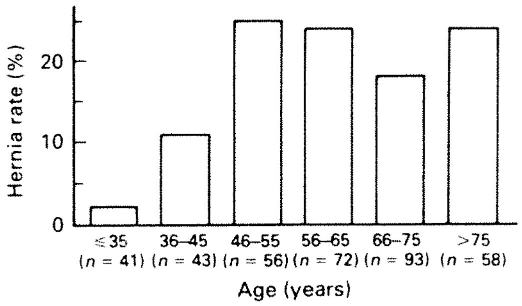

Figure 2 *Incidence of incisional hernia 12 months after operation in relation to patient age*

Table 1 *Comparison of patients with regard to suture length to wound length ratio*

	Ratio	
	≥4 (n=122)	<4 (n=241)
Mean age (years)	57	60
Sex ratio (M:F)	56:66	134:107
Previous midline operation (%)	26	22
Emergency operation (%)	30	25
Degree of contamination (%)		
Clean	36	39
Contaminated	52	54
Dirty	12	7
Wound infection (%)		
Minor	3	5
Major	5	3
Suture material (%)		
Polydioxanone	58	49
Nylon	42	51
Mean length of incision (cm)	26	27

There were no statistical differences between groups

Table 2 *Incidence of incisional hernia*

	Ratio	
	≥4	<4
Patients	122	241
Incisional hernias	11 (9·0)	57 (23·7)

Values in parentheses are percentages. $\chi^2 = 10{\cdot}45$, 1 d.f., $P = 0{\cdot}001$

Stepwise forward multiple linear regression analysis was performed, testing the suture length to wound length ratio, age, major wound infection and length of incision as predictors of hernia. Multivariate analysis identified the suture length to wound length ratio, age and major wound infection as independent risk factors, whereas wound length was not found to affect the incidence of hernia significantly.

Discussion

It has previously been proposed that the suture length to wound length ratio is associated with the incidence of complications of continuously sutured incisions[1,6,13–15]. The present results support this hypothesis, as a strong correlation between the ratio and subsequent incisional hernia was demonstrated (*Table 2*). A ratio <4 resulted in a 2·5-fold higher incidence of hernia than was found for wounds sutured with a ratio ≥4.

Concerning early complications, the incidence of wound infection did not correlate with the suture length to wound length ratio and patients with wound dehiscence were too few to permit analysis. The low incidence of dehiscence indicates that suture quality and basic surgical technique, such as suture handling and knotting, were adequate. Two instances of wound dehiscence occurred in patients with an extremely low suture length to wound length ratio; this should be regarded as a failure in suture technique.

The overall incidence of incisional hernia in the present study may seem high, but others have applied similar criteria of fascia healing 12 months after surgery and reported comparable rates[23–25]. Furthermore, with the liberal inclusion criteria used in the present trial, several factors considered to increase the risk of postoperative hernia were present in a substantial proportion of patients, including old age, incision through scar tissue, emergency operation, length of incision exceeding 18 cm, and major wound infection[4,26,27]. Of these, the present study identified a suture length to wound length ratio <4, age above 45 years and major wound infection as significant and independent risk factors. To date, 14 of the 68 patients (21 per cent) who developed hernia have needed operative repair. This shows that, although the definition of hernia was rather broad, a significant number of patients have already presented with symptoms severe enough to require surgical intervention.

An association between wound sepsis and incisional hernia has been reported by others[4]. It is an interesting finding in the present study that proper surgical technique may reduce the incidence of hernia even in this high-risk group of patients.

The suture length to wound length ratio depends on the size of tissue bites, the distance between bites and the tension on the suture. The relative importance of these factors for subsequent wound healing is uncertain, as clinical studies on this issue are few[16]. As the trial continues, it might be possible to assess the separate effect of these technical factors on clinical outcome.

An intervention was made in the trial when preliminary results became available in April 1991. Participating surgeons were then urged to adjust their suture technique towards a suture length to wound length ratio of 4:1. The compliance of the surgeons with these recommendations as well as possible benefits of altered technique will become evident as the study continues.

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Complications and survival of multilumen central venous catheters used for total parenteral nutrition

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In a prospective study of 879 triple-lumen catheters, 219 pulmonary artery catheters, 31 double-lumen and six single-lumen catheters used for the administration of total parenteral nutrition over a 1-year period, the overall complication rate was 12·5 per cent (14·7 complications per 1000 catheter-days) and the catheter-related sepsis rate 4·4 per cent (5·2 per 1000 catheter-days). The probability of development of catheter-related sepsis did not increase with the duration of catheterization. There were no differences in the rate of complications associated with 427 catheters changed by replacement at a new site compared with 159 lines changed over a guidewire. These data support the use of multilumen central venous catheters for the administration of total parenteral nutrition. They suggest that a routine weekly change of line is unnecessary; catheters should be changed only on the development of a complication. When it is required, a catheter should be changed by replacement over a guidewire.

The high concentration of dextrose, lipids and other nutrients in total parenteral nutrition (TPN) solutions increases the risk of septicaemia when central venous catheters are used for their delivery[1–3]. TPN is normally therefore delivered through a dedicated single-lumen central venous line[4]. Strict protocols regarding the use of such catheters are recommended by nutritional support teams[5,6].

Requirements for providing central venous access for the administration of fluids and medications, and for monitoring of central venous and left atrial pressure in critically ill patients, bring into question the necessity for a central venous line dedicated solely to the administration of TPN[1]. This study audited the complications associated with multiuse and multiuser central venous catheters employed for the administration of TPN solutions and the practice of routinely changing such catheters to minimize infective complications.

Patients and methods

Data including the type, site and method of placement were collected for all central venous catheters used for the administration of TPN between 1 November 1988 and 1 November 1989. On removal of the line, the duration of catheterization, the nature of any complication, the reason for removal and the results of culture of the catheter tip, and of peripheral and central venous blood cultures were recorded.

TPN was administered through 1135 percutaneously placed catheters, which comprised 879 triple-lumen devices, 31 double-lumen lines, six single-lumen catheters (Arrow-Howes 7 Fr; Arrow International Equipment, Reading, Pennsylvania, USA) and the side port of 219 pulmonary artery catheters (Swan–Ganz VIP catheter, 7·5 Fr; American Edwards, Anasco, Puerto Rico).

Central venous catheters were inserted at the bedside by physicians on the nutritional support team, by the staff of the intensive care units or by other physicians under the supervision of a member of the nutritional support team. The subclavian vein was cannulated in 528 instances and the internal jugular vein in 579. The external jugular vein was used for 24 central venous catheters, and four catheters were placed in the femoral vein.

The policy of the nutritional support unit was to change central venous catheters at the beginning of TPN therapy and thereafter only if complications developed. Patients managed on the intensive care unit underwent a routine change of line every 6 days, or more frequently if a change to a pulmonary artery catheter was required.

Only newly placed or changed catheters were used for the administration of TPN. One port of the central venous line was reserved for the administration of such nutrition. The administration of TPN was stopped until the line was changed if there was any possibility of contamination of the catheter by administration of unauthorized drugs. No restrictions were placed on the use of the other ports of multilumen central venous or pulmonary artery catheters, except that full aseptic technique was used for all catheter manipulations.

A site infection was defined as the presence of erythema around, or pus exuding from, a central venous line puncture site. Catheter-related sepsis was present when a culture of peripheral or central venous blood yielded the same organism as culture of the tip of the central venous line, as assessed by semiquantitative methods[7]. As catheter-related sepsis was a retrospective diagnosis, suspected sepsis was managed by one of two protocols. Patients with probable catheter-related sepsis, as defined by the development of a high fever with or without rigors in the absence of overt sepsis elsewhere, were managed by withdrawal of TPN, removal of the line, culture of the tip and simultaneous peripheral and central blood culture before the start of empirical antibiotic therapy. A new central venous line was placed, and TPN commenced 48 h after resolution of signs of sepsis. Patients with possible catheter-related sepsis, as defined by the exacerbation of a pre-existing fever and the development or worsening of cardiovascular instability, were managed by catheter change using the Seldinger technique or by replacement at a new site. If culture of the catheter tip and venous blood confirmed the presence of catheter-related sepsis, lines changed over a guidewire were removed. TPN was begun again after 48 h through a central venous line placed at a different site.

Statistical analysis

The duration of survival of catheters was analysed by Kaplan–Meier life-table analysis[8]. For the analysis of failure caused by catheter-related sepsis, lines were counted as failed on the day that they were removed for subsequently proved catheter-related sepsis; all other catheters were censored on the day of removal. For the analysis of failure from all complications, catheters were counted as failed if they had been removed for any complication and censored if they had been removed at the end of treatment or for a routine change. Log rank analysis[9] was used to determine statistical significance between life-table curves; significance was assumed for two-tailed $P < 0.05$.

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Results

TPN was administered to 563 patients through 1135 central venous catheters for a total of 9641 patient-days. The median period for which patients required TPN was 13 (range 2–156) days. The median time that catheters were left *in situ* was 7 (range <1–99) days (*Figure 1*). TPN was administered through a single line in 326 patients; the range of the number of catheters in the remaining 237 patients is shown in *Figure 2*.

The mortality rate for patients receiving TPN was 22·2 per cent; no death was attributable to TPN administration. The complication rate was 12·5 per cent (14·7 complications per 1000 catheter-days). Of the 1135 central venous catheters placed, 145 complications were recorded for 142 lines. Complications of insertion, i.e. pneumothorax, air embolism and malposition, occurred in 16 catheters (1·4 per cent). Late non-infective complications, principally dislodgement and blockage, occurred in 75 catheters (6·6 per cent). Infective complications were present in 54 lines (4·8 per cent). Catheter-related sepsis was present in 50 central venous lines (4·4 per cent; 5·2 per 1000 catheter-days) (*Table 1*). The tips of 17 catheters (1·5 per cent) grew the same organisms as those cultured from distant septic foci. The organisms isolated are shown in *Table 2*.

Complications occurred at a median of 7 (range <1–99) days. Life-table analysis for survival of catheters is shown in *Figure 3*. The probability of catheter-related sepsis developing was 0·4 per cent per day in the first week that a line was used, between 0·8 and 0·9 per cent per day between weeks 2 and 4, and zero in the fifth week.

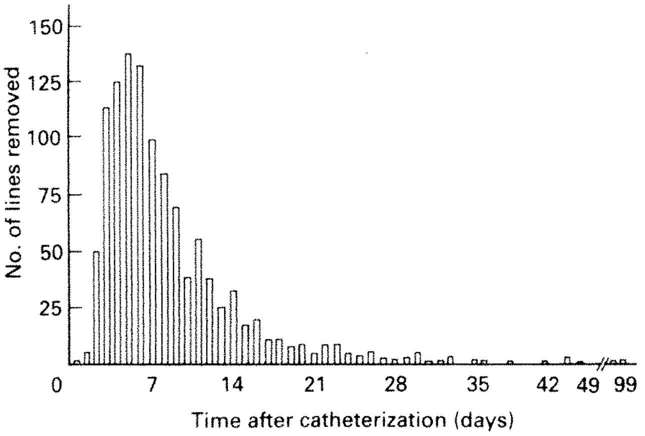

Figure 1 *Number of catheters removed according to time after catheterization*

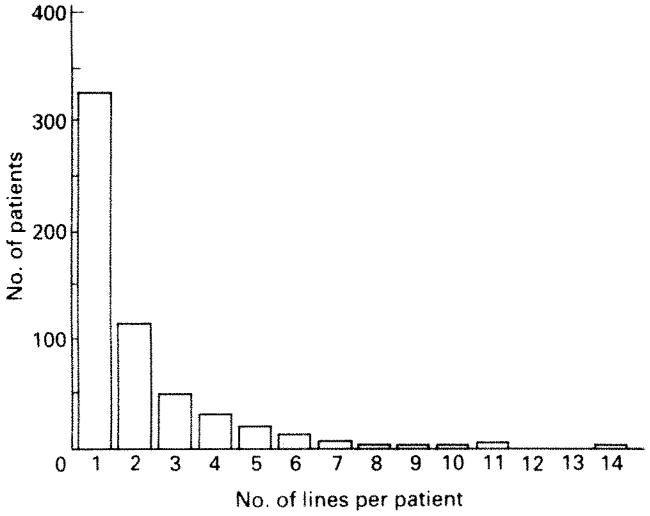

Figure 2 *Number of central venous catheters per patient*

Table 1 *Complications of 1135 central venous catheters*

Complication	No.
Cather-related sepsis	50 (4·4)
Site infection	4 (0·4)
Pneumothorax	8 (0·7)
Air embolism	1 (0·1)
Malpositioning	7 (0·6)
Thrombosis	7 (0·6)
Blocked line	19 (1·7)
Leakage	4 (0·4)
Dislodgement	45 (4·0)

Values in parentheses are percentages

Table 2 *Organisms isolated from the catheter tip and venous blood of patients with catheter-related sepsis*

Organism	No.
Coagulase-negative staphylococci	24
Staphylococcus aureus	6
Streptococcus group D	1
Klebsiella	3
Serratia	2
Enterobacter	5
Torulopsis glabrata	1
Candida albicans	8
Candida tropicalis	3

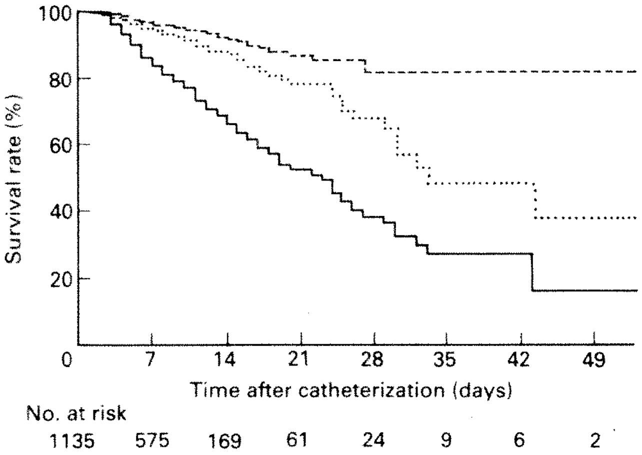

Figure 3 *Life-table analysis of the survival of central venous catheters. Analysis by failure caused by catheter-related sepsis (- - -), mechanical complications (·····) and all complications (——)*

Table 3 *Indications for change of central venous catheters*

Indication	Guidewire	New site	Total
Before the start of TPN	49	0	49
Routine change	52	224	276
Change type of catheter	12	83	95
Possible catheter-related sepsis	24	76	100
Catheter leakage	1	3	4
Dislodgement	6	20	26
Central venous thrombosis	0	4	4
Malpositioning	4	2	6
Blocked line	6	11	17
Line protocol violation	5	4	9
Total	159	427	586

TPN, total parenteral nutrition

Table 4 *Complication rates for central venous catheters changed by new puncture and guidewire*

Complication	Guidewire (*n* = 159)	New site (*n* = 427)	Total (*n* = 586)
Catheter-related sepsis	5 (3·1)	22 (5·2)	27 (4·6)
Site infection	0 (0)	2 (0·5)	2 (0·3)
Pneumothorax	0 (0)	1 (0·2)	1 (0·2)
Air embolism	0 (0)	1 (0·2)	1 (0·2)
Malpositioning	4 (2·5)	2 (0·5)	6 (1·0)
Thrombosis	2 (1·3)	1 (0·2)	3 (0·5)
Blocked line	2 (1·3)	9 (2·1)	11 (1·9)
Leakage	1 (0·6)	1 (0·2)	2 (0·3)
Dislodgement	10 (6·3)	9 (2·1)	19 (3·2)
Total	24 (15·1)	48 (11·2)	72 (12·3)

Values in parentheses are percentages. The difference in complication rate between guidewire and new site change was not significant

Guidewire change of central venous line was performed on 159 occasions, either at the beginning of TPN or when treating any complication except catheter-related sepsis or site infection. Central venous catheters were changed through a new percutaneous site on 427 occasions; the indications for change are given in *Table 3*. There were no differences in the complication rate for central venous catheters changed over a guidewire compared with rates for those inserted through a new percutaneous site (*Table 4*). There was no difference in the rates of failure from catheter-related sepsis or any complication of catheters changed by guidewire compared with those of lines placed by a new puncture.

Discussion

The data presented show that the use of multilumen central venous catheters for the administration of TPN solutions in addition to intravenous fluids and drugs is safe. The data compare favourably with those of others, who have reported catheter-related sepsis rates of 2·8 per cent[10], 3·8 per cent[11], 5·7 per cent[12], 6·8 per cent[13] and 7 per cent[14] for single-lumen central venous catheters used for TPN under the supervision of a nutritional support team. The complication rates are higher for triple-lumen than for single-lumen devices. In a prospective study of 2431 lines, the catheter-related sepsis rate was 6·9 per cent for triple-lumen compared with 0·4 per cent for single-lumen central venous catheters[3]. A retrospective study of 496 central venous lines reported a catheter-related sepsis rate of 4·9 per cent for triple-lumen compared with 1·6 per cent for single-lumen devices[2]. A catheter-related sepsis rate of only 1·3 per cent was found for triple-lumen central venous catheters used for TPN compared with 0 per cent for single-lumen lines[15]. One study, however, supported the use of triple-lumen catheters, reporting a 7·9 per cent catheter-related sepsis rate for single-lumen compared with 3·8 per cent for triple-lumen devices[1].

Triple-lumen lines may be more prone to the development of catheter-related sepsis because they are manipulated more often than single-lumen devices. A sixfold increase in the catheter-related sepsis rate was reported for single-lumen catheters that had been ‘violated’ by the administration of drugs[14]. One study, however, reported no increase in the catheter-related sepsis rate for lines used variably for monitoring, antibiotic administration and withdrawal of blood[2]. In the prevention of sepsis, the care with which the catheter is handled is more important than the number of times it is manipulated.

Prophylactic changing of central venous lines to reduce the incidence of catheter-related sepsis is widely practised. Such sepsis is rare within 4 days of catheter placement[3] and this justified the practice of routine change of central venous catheters every 3–5 days[16–18]. The present data confirm that the probability of catheter-related sepsis does not increase with the duration of catheterization[19]. For a patient requiring TPN for 18 days, the sum of the probability of catheter-related sepsis for each of three lines changed at 6-day intervals is no different from the probability of sepsis in a single catheter left *in situ* for the whole period. These data are supported by a recent prospective randomized study of central lines which showed no difference in the rates of catheter-related sepsis in patients in whom catheters were changed every 3 days compared with those in whom lines were replaced as clinically indicated[20]. The practice of changing catheters places the patient at an increased risk of complications because of the greater number of attempts at catheterization. Catheters should therefore be changed only on the development of a complication[21].

Central venous catheters may be changed by replacement at a new site or by exchange over a guidewire[13]. The use of a different site avoids the risk of placing the new catheter through a colonized wound or of transferring intraluminal organisms to the new catheter by contaminating the guidewire in the course of the exchange. The technical complications of a catheter placed by new puncture are increased fourfold (8·8 *versus* 2·2 per cent) over those of exchange over a guidewire[20,22]. The present data show no difference in rates of catheter-related sepsis and of site infection for lines changed by either technique. Change of central venous catheters over a guidewire is therefore safe[23] provided the line is removed if subsequent investigation proves that catheter-related sepsis is present.

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Announcement

European Surgical Fellowships

The Council of *The British Journal of Surgery* is pleased to announce the availability of European Surgical Fellowships for 1994. Last year four Fellowships were awarded, to Dr Jose Luis Aguayo-Albasini (Spain), Mr R. M. Charnley (Nottingham), Mr S. D. Heys (Aberdeen) and Mr T. G. John (Edinburgh).

It is Council's intention to offer European Surgical Fellowships again in 1994. Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the UK to visit centres in other European countries or surgeons working in other European countries to visit the UK. Applicants must be under 40 years of age and should submit details of their proposed itinerary and its anticipated cost, together with a copy of their *curriculum vitae* and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, by 1 February 1994.

D. C. Carter

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On-scene medical decision making and overtriage

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This study examined whether a hospital-based helicopter trauma service led to 'overtriage' of patients back to the multispecialty base hospital. All accident-site triage decisions made during 1991 were studied. Seven of the 574 decisions (1·2 per cent) led to inappropriate movement of the patient to a specialist centre. Twenty-six decisions (4·5 per cent) were based on mechanism of injury alone and the possibility of overtriage by this method is discussed. A trained doctor can select the correct destination for a patient with trauma without inappropriately using the base hospital in preference to local centres.

Considerable benefit is gained by transporting the trauma patient directly from the accident scene to a hospital with the necessary specialist facilities for treating major injuries rather than to the nearest hospital[1]. Doctors involved in prehospital care have the opportunity to make decisions regarding the optimum hospital destination. This triage is most important in urban areas, where there may be large numbers of accident and emergency units in close proximity with a varying range of associated specialties. Factors important in correct triage are: (1) mechanism of injury; (2) the patient's physiological state; (3) the injuries themselves; (4) specialist facilities available in each of the nearby hospitals; and (5) likely transport times.

The initial protocol for the Helicopter Emergency Medical Service (HEMS) operation intended that severely injured patients would be picked up from anywhere within the four Thames Regions[2]. Patients were transported to the nearest hospital with appropriate facilities to treat their injuries, a decision taken at the incident scene by the HEMS registrar. This study was designed to assess whether triage decisions at the scene led to unnecessary transport to a specialist centre.

Many American trauma systems use triage protocols to enable paramedics to decide hospital destination. Coding of initial clinical observations, mechanism of injury and site of apparent injuries[3–6] has led to the development of a large number of methods such as the Trauma Score[7], the Triage Revised Trauma Score[8], the CRAMS (circulation, respiration, abdomen, motor and sensory) score[9], the Pre-Hospital Index[10], the Revised Trauma Index[11] and the Trauma Triage Rule[12,13]. Details of these protocols vary, but most result in patients with the following criteria being transported to a trauma centre:

1. High-speed (>40 m.p.h.; > 65 km/h) moving vehicle accident.
2. Pedestrian hit by vehicle at more than 20 m.p.h. (30 km/h).
3. Ejection from vehicle.
4. Fall from height >20 feet (6 m).
5. Penetrating injury to head, neck, chest, abdomen, pelvis or groin.
6. Blunt injury with significant involvement of head, neck, chest, abdomen or pelvis.
7. Two or more proximal long bone fractures.
8. Blood pressure <100 mmHg.
9. Respiratory rate >29 or <10 per min.
10. Glasgow Coma Score (GCS) ⩽10.

Failsafe protocols are considered vital in America to ensure that patients are 'overtriaged' to trauma centres[14]. This practice reduces the overall mortality rate[15], but many of these referrals are unnecessary[16–18] as patients often have only minor trauma despite a severe mechanism of injury[19]. The judgement of American ambulance personnel may be as effective as scoring systems in selection of the seriously injured[20]. The involvement of a doctor leads to selection of a group of patients with significantly higher median Injury Severity Score (ISS)[21]. These American criteria, developed for use by paramedics, may not be ideal for decision making when an early assessment is made by an appropriately trained doctor, especially in the context of London's extensive supply of accident and emergency departments.

Medical decision making was examined to assess triage at the incident scene, analyse the factors essential in the choice of hospital destination and determine whether overtriage to the base hospital took place.

Patients and methods

Prehospital notes of all patients attended by HEMS during 1991 were examined, and the nearest hospital and receiving hospital recorded. If the patient was not taken to the nearest hospital, the initial observations and Abbreviated Injury Score (AIS) for each body area were recorded.

The registrars in the helicopter service are provided with a computer-generated specialty specification of the hospital nearest to any incident attended. The nearest burns unit, neurosurgical unit and multispecialty hospital are also given. The specialties are matched against the patient's injuries and, with local knowledge from ambulance crews about traffic conditions and possible obstructions, the treatment centre is chosen. A triage decision to transport the patient away from the nearest hospital was considered correct in the following circumstances:

1. GCS <12 with no neurosurgery unit at the nearest hospital.
2. Burns >15 per cent with no burns unit at the nearest hospital.
3. Severe chest injury (chest AIS ⩾3) with no cardiothoracic unit at the nearest hospital.
4. Severe facial injury (face AIS ⩾3) with no maxillofacial unit at the nearest hospital.
5. Spinal injury (spine AIS ⩾3) with no specialist unit at the nearest hospital.
6. If the HEMS registrar recorded logistic reasons, such as: (a) the travelling time was significantly less by air than by land; (b) the patient was being airlifted from an inaccessible position when the local hospital had no landing site; or (c) there was a barrier such as traffic, roadworks, or accident debris preventing access to the local hospital, and the local hospital had no helipad.

Patients who did not fall into these categories were examined and outcome recorded.

Results

Of 574 patients assessed by the HEMS registrars, 373 (65 per cent) were triaged to the local accident and emergency department; 104 (18 per cent) of these patients had injuries severe enough to warrant medical escort by the HEMS doctor. Of the 201 patients (35 per cent) taken to a hospital that was not the nearest to the incident scene, 161 (28 per cent) were transferred to the multidisciplinary centre at the Royal London

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Hospital and 40 (7 per cent) to other specialist centres (*Figure 1*).

Reasons for the triage decisions in the 201 patients not taken to the hospital nearest to the incident scene are shown in *Table 1*. Three of the four patients who were incorrectly triaged had severe head injuries and were moved to the Royal London Hospital, although the local hospital had neurosurgical specialists. The fourth patient had suffered a gunshot wound to the left groin and was incorrectly triaged in the misplaced belief that local traffic difficulties would prevent immediate transfer to a closer centre by road.

Twenty-six patients (4·5 per cent) were transported to specialist centres because of the mechanism of injury; one of these died. The ISSs for these patients are shown in *Figure 2*. No data were available for three patients as injury severity scoring was not performed at the centres to which they were taken.

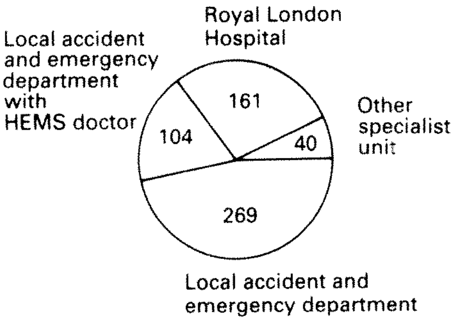

Figure 1 *Destination of 574 consecutive Helicopter Emergency Medical Service (HEMS) patients*

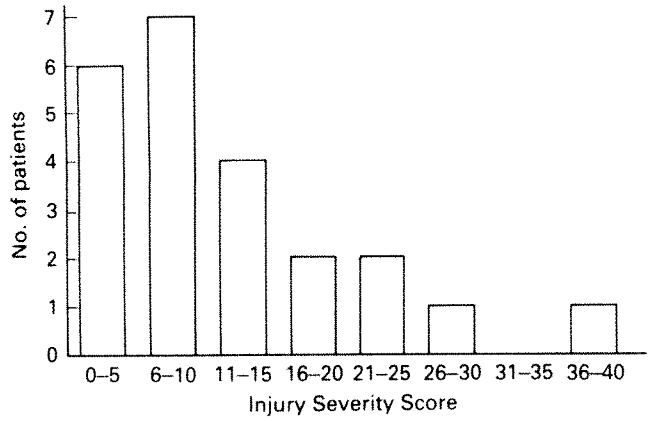

Figure 2 *Injury Severity Scores of patients transported on the basis of mechanism of injury*

Table 1 *Reasons for patient distribution in 201 patients not taken to the local hospital*

Reason	No. of patients
GCS < 12 with no local neurosurgery unit	120
Burns > 15% with no local burns unit	15
Severe chest injury with no local thoracic unit (thorax AIS ≥ 3 in 4)	5
Severe facial injury with no local maxillofacial unit (face AIS ≥ 3 in 2)	2
Spinal injury with no local specialist unit (spine AIS ≥ 3 in 7)	9
Logistic	8
Mechanism of injury	26
Incorrect triage	4
Field surgery, continuity of care	2
Data not available	10

GCS, Glasgow Coma Score; AIS, Abbreviated Injury Score

Discussion

It is known that taking a patient direct to the appropriate specialist centre leads to the best outcome[22,23]. The 148 patients in the present study with burns or head, chest, facial or spinal injury taken to the appropriate specialist centre are therefore not discussed further.

Three patients (0·5 per cent) were thought to require specialist treatment (two with spinal and one with thoracic injury) but were subsequently found not to have severe trauma (AIS ≤ 2). In retrospect, a further four (0·7 per cent) of the triage decisions were incorrect because the local hospital had all the facilities to treat the injuries and there was no logistic reason why transport to the nearest hospital should have been difficult. The only death in this group was from a severe head injury (AIS 5).

For 26 patients (4·5 per cent), the decision to transport to a specialist centre was based on mechanism of injury. The only death in this group followed blood loss in a patient with multiple fractures who refused transfusion on religious grounds. Only seven of these patients had severe injuries (ISS > 16) and none needed facilities not available in the local hospital. Mechanism of injury appears to be only 25 per cent specific for severe trauma in patients who are fully conscious with no initial haemodynamic or respiratory compromise and does not predict those requiring specialist treatment. In the only comparable series[24], an Italian helicopter medical team, using triage decisions heavily weighted for mechanism of injury, had an overtriage rate of 38 per cent. The present series, however, is too small to refute the large body of evidence supporting the importance of mechanism of injury[25]. The 26 patients moved on the basis of mechanism of injury were therefore triaged correctly according to protocol. In retrospect they may not have been appropriate patients for a multidisciplinary centre. In Britain it is not yet known whether patients with ISS > 16 who do not need specialist intervention (i.e. have a combination of orthopaedic and general surgical injuries) benefit from transport direct to a multidisciplinary centre, and no definite statement can be made as to whether these patients were overtriaged. There was a small bias towards moving the patient to a multidisciplinary centre rather than to a potentially inappropriate local hospital; this acts in the patient's best interests as there is no evidence of harm resulting from inappropriate movement to a specialist centre. In contrast, an inappropriate primary journey to a non-specialist hospital could result in long delays and possible secondary transfer before definitive intervention, with poor patient outcome[26].

Information about undertriage, i.e. patients taken to the local accident and emergency department when direct transport to a specialist centre would have been more appropriate, will not be available until the formal report on HEMS from the assessment team at the University of Sheffield. Such data are required for full analysis of triage criteria[27].

In spite of tensions and anxieties associated with medical intervention at the accident site, appropriately trained medical staff were able to triage patients effectively and, on medical criteria, inappropriately moved patients to the base hospital in only 1·2 per cent of missions. The use of mechanism of injury as a triage tool in the selection of patients for transfer to a specialist centre raised the overtriage rate to 5·7 per cent but this is likely to be in the patients' best interests.

Accident-site triage by an appropriately trained doctor, in conjunction with information from local ambulance crews, selects patients who will benefit from transport directly to a facility specializing in trauma management without significant inappropriate movement of those who could have been managed locally.

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Acute haemodilution in surgery for burns: a preliminary report

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Blood loss is a major problem in the management of patients with burns treated by early excision and grafting. Acute normovolaemic haemodilution has been successfully used in cardiac surgery for many years but has not been reported previously in surgery for burns. The technique has been used in six patients with burns undergoing early excision and grafting, with no obvious morbidity and an apparent reduction in homologous blood requirements.

The advantages of early tangential excision and split-skin grafting for deep dermal and full-thickness burns are well established, particularly with regard to reduction in the length of hospital stay[1]. Blood loss associated with this technique may limit the extent of surgery to excision of between 10 and 30 per cent of body surface area burn, depending on whether tourniquets can be used[2]. The morbidity of homologous blood transfusion is well documented and new risks are constantly being identified[3,4]. Children are at particular risk because of their long expected lifespan after transfusion[5]. They also form the majority of patients suitable for early burn excision and grafting.

Acute haemodilution has been widely practised in cardiac surgery for over 20 years but, despite its increasing use in vascular and general surgery, has not previously been applied to surgery in the treatment of burns.

Patients and methods

Hospital Ethics Committee approval was gained for the study protocol and written consent obtained from the patient or guardian before surgery. Patient selection was based on a likely need for blood transfusion and the guidelines for autologous transfusion issued by the Blood Transfusion Task Force of the British Committee for Standards in Haematology[6]. The final decision on whether to proceed with harvest was made by the consultant anaesthetist (P.T.) and surgeon (F.B.B.). Monitoring included electrocardiography, measurement of blood pressure (using a cuff or direct measurement) and central venous pressure, and pulse oximetry. The volume of blood to be harvested was calculated as 10 ml/kg with monitoring by use of serial haematocrit measurements.

Blood harvest was started only when the patient was anaesthetized and awaiting surgery. An initial on-table haematocrit of at least 30 per cent was required before proceeding. Blood harvest and samples were taken from a central venous line with the patient in a 10° head-down position. The volume of blood harvested was replaced over 5 min with a similar volume of Hartmann's solution and the haematocrit remeasured. If the haematocrit was still greater than 30 per cent, further blood was harvested as necessary.

Surgery then proceeded and the harvested blood was returned when 10 per cent of circulating blood volume had been lost during operation. All the autologous blood was restored by, or shortly after, completion of surgery; any further requirements were satisfied using homologous blood. Prior consent was obtained to dispose of the harvested blood should any contraindication to its reinfusion have arisen. The only additional facilities required were a dedicated supervisor for the harvest and the taking of samples for haematocrit measurements, and the presence of a pressurized bag of Hartmann's solution, connected to the central line, for infusion in the event of sudden circulatory collapse.

Results

Details of the patients studied are given in *Table 1*. Observations of pulse, blood pressure and central venous pressure in all six were within 10 per cent of reference values throughout the procedure. After the first two patients, harvesting of the blood and volume replacement added approximately 15 min to the duration of the procedure.

Table 1 *Patient details*

Patient no.	Age (years)	Sex	Burn type	Burn site	Body surface area (%)	Area excised (cm²)
1	11	M	Flame	Upper arm	4	360
2	21	F	Contact	Trunk	3	550
3	23	M	Contact	Arm	6	550
4	13	M	Flame	Hands, legs	30	2510
5	30	F	Scald	Trunk	18	1060
6	48	M	Flame	Trunk, legs	45	1520

Estimated blood loss, autologous and homologous transfusion volumes, and the calculated and actual changes in haemoglobin concentration during the perioperative period are given in *Table 2*.

Blood volume calculations were based on a blood volume of 75 ml/kg, with the exception of patients 2 and 5, who were both female with a significant covering of body fat and in whom a volume of 70 ml/kg was used. Patients 5 and 6 required homologous transfusion (2 and 4 units red cells respectively).

Expected postoperative haemoglobin concentrations were calculated as the difference between the total haemoglobin lost and the total at the start of the procedure as a concentration in the blood volume calculated from body-weight. Patient 2 had a higher haemoglobin concentration on admission (14·4 g/dl) and slight haemodilution may have occurred after induction of anaesthesia, resulting in the postoperative haemoglobin level being above the immediate preoperative value and the large operative 'gain'.

No intraoperative or postoperative complications were observed.

Discussion

There is a definite, albeit low, morbidity associated with homologous blood transfusion and it is therefore desirable to minimize or avoid such transfusion when possible[3,4]. Acute haemorrhage induces hypercoagulability, which homologous transfusion is reported to diminish[7]. This may be of significance in surgery for burns, where blood loss results from widespread oozing from a large number of capillaries rather than from a small number of larger vessels. Other factors influencing the indications for homologous transfusion are the acceptable haemoglobin level, the timing of transfusion and the availability of the patient's own red cells.

There has been much debate on the acceptable concentration of haemoglobin, but most investigators consider levels of between 8 and 9 g/dl to be safe[8]. Rush *et al.*[9] confirmed the reliability of changes in the haematocrit as an index for

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Table 2 *Perioperative blood changes*

		Blood volume (ml)				Haemoglobin level (g/dl)			
Patient no.	Body-weight (kg)	Harvest	Calculated circulating	Operative loss	Operative 'gain'	Preoperative	Minimum	48-h postoperative	Calculated postoperative
1	45·4	450	3405	750	448	11·4	8·5	10·4	8·9
2	91·2	900	6384	700	1073	11·3	8·8	12·0	10·1
3	80·0	900	6000	900	360	10·0	7·1	9·1	8·5
4	69·4	900	5205	1070	490	11·7	9·3	10·4	9·3
5	59·4	900	4158	1750	309	12·1	7·0	11·2	10·3
6	78·2	1350	5865	2700	−512	12·6	7·6	10·2	11·3

replacement of blood with electrolyte solutions and its usefulness in providing an endpoint for beginning the use of blood.

Autologous blood may be obtained from three sources. Elective predonation is not applicable to early surgery for burns, and intraoperative and postoperative cell salvage is considered hazardous when the blood has been exposed to bacterial contamination[10].

Acute haemodilution with harvesting of 25–30 per cent of the patient's blood volume has become established practice in cardiac surgery after an initial report[11] in 1968. A literature search has revealed no previous reports of the use of this method in early surgery for burns. Acute haemodilution has now been safely undertaken in such patients in a controlled situation with no obvious morbidity in this small number. The majority of patients undergoing surgery for burns are young, with many years to develop the complications of homologous transfusion[12]. Used in combination with methods of reducing blood loss and requirements, acute haemodilution could enable the avoidance of homologous transfusion in many of these patients.

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Early wound excision and skin grafting restores cellular immunity after severe burn trauma

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Suppression of cellular immunity following thermal injury may contribute to the high incidence of postburn sepsis. Early excision and skin grafting may remove deleterious local wound factors and prevent immunosuppression. The effect on cellular immunity of early burn wound excision and skin grafting was investigated in an animal model using female Wistar rats. The development of immunosuppression shortly after burn injury was shown by popliteal lymph node assay and a 2,4-dinitrofluorobenzene skin reaction test. Excision and skin grafting 2 days after burn trauma restored parameters to normal. Burned tissue suppresses cellular immunity; this effect is preventable by early excision and skin grafting.

Patients exhibit a wide variety of immunological changes following thermal injury. Impaired neutrophil function, a reduced T helper:T suppressor ratio, decreased lymphocyte blastogenesis in response to mitogens, impairment of interleukin 2 production and the presence of circulating suppressive factors have been implicated in the pathophysiology of immunodepression related to burn injury[1–9].

Since the early work of Meeker and Snyder[10] the beneficial effects on morbidity and mortality rates of early excision and skin grafting have been reported[11–14]. There are, however, few *in vivo* controlled studies evaluating cellular immunity following early excision and skin grafting. The present study examined the effect of early excision and grafting on popliteal lymph node assays and 2,4-dinitrofluorobenzene skin reaction tests as measures of cellular immune competence.

Materials and methods

Animals and surgical techniques

Female Wistar rats weighing 180–200 g were caged in groups of three at ambient room temperature, and given water and food *ad libitum*. After acclimatization for 1 week the animals were randomized to four groups: sham-burned controls (group 1), burned (group 2), burned with early excision and skin grafting (group 3), and excision and skin grafting without burn injury (group 4). Group 1 comprised ten animals that were anaesthetized and shaved but not scalded. Group 2 animals ($n = 72$) were randomized into six subgroups of 12 each to study responses on days 1, 4, 7, 10, 14 and 21 after burn. Group 3 rats ($n = 60$) underwent early excision and skin grafting at 48 h. Animals in this group were randomized into five sets of 12 to evaluate immune responses on days 4, 7, 10, 14 and 21 after thermal injury. On the designated days for each group, wounds were completely excised and the defects closed with a split-thickness graft from a Lewis rat. Group 4 consisted of ten rats that were not given thermal injury but underwent the same percentage skin excision and grafting.

Burn model

Animals were anaesthetized with pentobarbital 45 mg kg^{-1}. The back and abdomen were shaved. The rats were placed in a mould that left 30 per cent of the total body surface area exposed and this surface immersed into a water bath at 95°C for 10 s. Animals were then resuscitated with Ringer's lactate solution 6 ml intraperitoneally.

Contact hypersensitivity

Rats were sensitized by the application of 100 μl 0·5 per cent 2,4-dinitrofluorobenzene (Sigma Chemicals, St Louis, Missouri, USA) in 4:1 acetone:olive oil on the shaved abdomen on days 1, 4, 7, 10, 14 and 21 after burn. Some 5 days later the animals were challenged by application of 2,4-dinitrofluorobenzene to the ears. Ear swelling was measured using calipers after 24 h and the results expressed as a percentage of swelling in controls (group 1).

Popliteal lymph node assay

This was accomplished using a previously described method[15]. Splenocytes from Sprague–Dawley rats were given to Wistar recipients for the host *versus* graft reaction. Splenocyte suspensions were prepared by mincing the pulp into a balanced salt solution. Erythrocytes were lysed with Tris–NH_4Cl. Suspensions were washed twice and the cells resuspended in balanced salt solution to a concentration of 20×10^7 viable cells per ml (trypan blue exclusion assay). In 0·1 ml, 20×10^6 viable cells were injected into the right hind footpad of the recipient. After 5 days the recipients were anaesthetized and the popliteal lymph nodes from both hind legs removed and weighed. Popliteal lymph node enlargement in response to antigenic challenge in each recipient was evaluated using the ratio of injected to uninjected node weight.

Statistical analysis

Data are presented as mean(s.e.m.). Statistical significance was assumed at $P < 0·05$ and determined by Student's t test.

Results

A total of 23 rats (17·4 per cent) died within 72 h after injury; sham burn, and early excision and skin grafting without previous burn injury resulted in no mortality. Clearly demarcated full-thickness third-degree burn eschars were obtained within 48 h. These then gradually sloughed in 15–25 days. The wounds did not become grossly infected and healed over a 3–4-week period by contraction and skin growth from the wound edges.

Compared with normal controls (group 1) the mean(s.e.m.) contact hypersensitivity response to 2,4-dinitrofluorobenzene in group 2 (97·1(1·1) per cent) was inhibited by burn injury. The mean(s.e.m.) ear swelling was significantly reduced in response to application of 2,4-dinitrofluorobenzene on days 7 (33·5(2·9) per cent) and 10 (20·0(4·3) per cent) ($P < 0·001$). By 21 days after burn the wounds were largely healed in most animals and response to 2,4-dinitrofluorobenzene (89·4(5·0) per cent) had returned to nearly normal levels.

Early wound excision and skin grafting at 48 h after burn injury improved response to 2,4-dinitrofluorobenzene in group 3 to levels comparable to those of controls. Waiting more than 48 h before early excision and skin grafting resulted in a decreased improvement (*Figure 1*); deterioration in immune status was directly proportional to the waiting period. The contact hypersensitivity response in this group returned to normal levels on day 21 after thermal injury. Immunosuppression as measured by the 2,4-dinitrofluorobenzene skin test was minimal (mean(s.e.m.) 91·4(4·6) per cent) in group 4 animals.

The mean popliteal lymph node weight in uninjected controls was 41·2 mg. Following the injection of splenocytes

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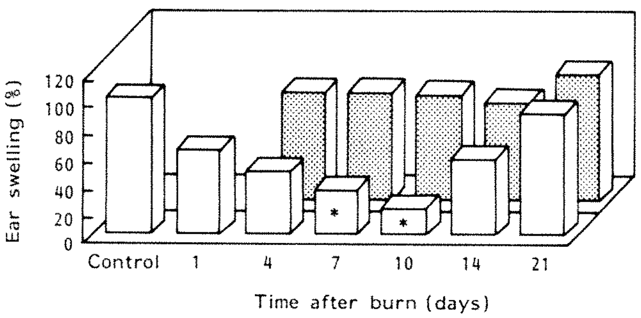

Figure 1 *Mean contact hypersensitivity reaction to 2,4-dinitrofluorobenzene at different times after burning.* □, *30 per cent burn injury;* ▨, *30 per cent burn injury with early excision and skin grafting.* *$P < 0\cdot001$ (*days 7 and 10* versus *controls, Student's* t *test*)

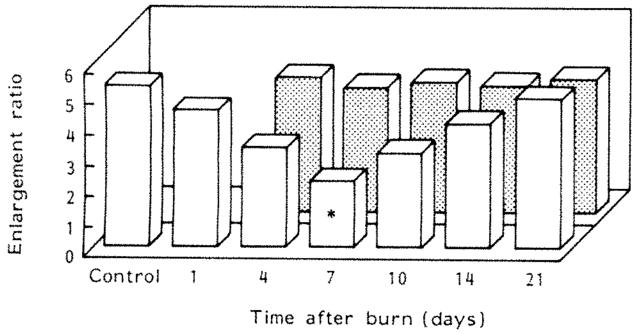

Figure 2 *Popliteal lymph node assay. Enlargement following standard injection of spleen cells is expressed as the mean ratio of the weight of injected to uninjected nodes.* □, *30 per cent burn injury;* ▨, *30 per cent burn injury with early excision and skin grafting.* *$P < 0\cdot001$ (*day 7* versus *controls, Student's* t *test*)

the peak mean(s.e.m.) enlargement ratio in unburned rats (group 1) was found to be 6·0(1·0). This value was indicative of severe immunodepression, which became worse at day 7 (2·2(0·3)) ($P < 0\cdot001$) in burned group 2 rats. Immediate early excision and skin grafting after burning in group 3 resulted in a return of the popliteal lymph node assay response toward normal levels, although the values remained reduced from those of group 1 (*Figure 2*). No significant immunodepression was demonstrable in group 4: at 4, 7, 10, 14 and 21 days after thermal injury the respective mean(s.e.m.) enlargement ratios were 4·5(0·9), 4·1(0·7), 4·3(0·3), 4·2(0·3) and 4·5(0·7).

Discussion

Thermal injury leads to an immunosuppressed state and renders the burned host more susceptible to sepsis[8,16,17]. The pathophysiology of postburn immunosuppression involves specific cellular and humoral defects[2,9]. Removal of either the burn wound or cellular elements of the immune system from the burned host improves cellular immune function[18–20]. These findings suggest that the burn wound might be the major factor responsible for immunosuppression after thermal injury. Delayed-type skin reaction tests and popliteal lymph node assay are accepted methods for quantitative *in vivo* monitoring of immune status. The contact hypersensitivity skin test has been shown in previous experiments[21,22] to be a sensitive and quantifiable measure of cellular immunity. The popliteal lymph node assay is an established method that reflects *in vivo* mixed lymphocyte reactions and permits the evaluation of host *versus* graft responses[20,22,23].

The results of the present study indicate that immune function gradually deteriorates beginning from day 1 after burning and reaching a trough between days 7 and 10. Immune function then gradually returns to normal levels, becoming almost normal on day 21. During this period diminished immune responsiveness measurable by popliteal lymph node assay and 2,4-dinitrofluorobenzene skin test was not accompanied by any gross quantitative cellular abnormality. These findings are in agreement with previous reports[9,24] but contrary to the results of Piacentine *et al.*[22], who found maximal immunosuppression to occur on day 14 after burning.

Numerous human studies favour early aggressive wound excision and skin coverage[10,12–14]. Controlled prospective trials in humans are difficult because of the presence of many variables (e.g. age, sex, extent of injury) and ethical issues.

Full-thickness burns of 20 per cent total body surface area are necessary for detectable immunosuppression[25]. Using such models of burn injury leads to increased suppressor T cell activity[8], a decreased helper:suppressor T cell ratio[26], diminished delayed hypersensitivity[20,22,27], a decreased lymphocyte blastogenesis response[28] and increased susceptibility to infection[9,29].

The present experiments simultaneously investigated the effect of burn, early excision and skin grafting, and burn with early excision and grafting on immune responsiveness. The degree of immunosuppression following burn with early excision and skin grafting was not significantly different from that observed in groups 1 and 4. This indicates that immunosuppression in group 3 most probably related to the effect of early excision and skin grafting itself. This is supported by previous data on the immunosuppressive effect of early excision and skin grafting, and other operations without preceding burn injury[30,31].

The continued presence of burned tissue is a major aetiological factor for immunosuppression that can be avoided by early excision and skin grafting.

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Axillary nodal metastases from an occult primary consistent with breast carcinoma

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The records of 15 women presenting with axillary nodal metastases from an occult primary consistent with breast carcinoma were reviewed. Nine patients underwent complete axillary clearance and in six the clinical mass only was excised. Radiotherapy to the axilla was given to eight patients. One woman underwent mastectomy at the time of axillary surgery but no tumour was found in the excised breast; in the remaining 14 patients the breast was left untreated. One premenopausal woman received adjuvant systemic chemotherapy and one postmenopausal patient was given tamoxifen. Three patients died from recurrent disease at 16, 50 and 56 months after treatment of the axillary mass; one is alive at 42 months with systemic recurrence. In two of these patients the tumour in the breast became apparent before other metastases. Eleven patients survived for a median of 92 (range 18–144) months without evidence of disease. The prognosis of this patient group is better than that generally reported for stage II breast carcinoma.

The metastatic enlargement of axillary lymph nodes may be the first sign of occult carcinoma of the breast[1,2]. Treatment has consisted of axillary surgery and mastectomy[1,3–7] but in a number of patients the primary tumour was not found in the breast specimen. Two recent studies demonstrated that patients treated with radical radiotherapy to the breast have the same prognosis as those who undergo mastectomy[2,6]. When the breast is left untreated the survival rate of the patients does not decrease[2,5,7,8]. In the present report, 15 women presenting with axillary nodal metastases from an occult primary consistent with breast carcinoma are described; in 14 the breast was left untreated.

Patients and methods

Between July 1980 and February 1991, 15 women were referred with a diagnosis of metastatic adenocarcinoma of the axilla from an unknown primary site. The histopathological findings of all axillary masses were consistent with breast carcinoma. On initial clinical examination none of the patients had a distinct palpable primary breast mass. One woman had undergone lumpectomy 3 months previously but review of the histopathology confirmed the diagnosis of a benign breast lesion. All patients underwent mammography and in two a suspicious lesion was seen. Localization biopsy, however, demonstrated benign lesions.

Many investigative procedures were carried out in 11 of the 15 patients in an attempt to find the primary tumour. In four patients only mammography, chest radiography, liver ultrasonography and bone scintigraphy were performed. In three patients ipsilateral supraclavicular node metastases were noted concurrently. In two patients contralateral breast carcinoma had been treated 8 and 11 years before the present axillary mass. One of these patients had been treated by lumpectomy, axillary clearance and irradiation of the breast (45 Gy, iridium boost 25 Gy) and parasternal area (45 Gy). The other had been treated by simple mastectomy and axillary clearance followed by irradiation of the parasternal area (45 Gy). Both tumours were classified as $pT_1 N_0$. One patient with a diagnosis of stage I malignant lymphoma in the right groin had been treated with irradiation and chemotherapy 3 years before presentation with adenocarcinoma of the axillary node.

Local treatment

Axilla. Nine patients underwent complete axillary clearance with the specimen containing a median of 2 (range 1–6) metastatic lymph nodes. In six patients the clinical mass only was excised. Additional radiotherapy to the axilla and supraclavicular area was given to eight patients (five of nine after axillary clearance, three of six after local excision). Radiation therapy was given with megavoltage equipment using standard techniques: four doses of 50 Gy and four of 40·5 Gy were delivered. In three patients a booster dose of 20 or 30 Gy was given for supraclavicular lymph node metastasis. One patient with five positive nodes in the axillary specimen was offered radiation therapy but refused.

Breast. Only one patient underwent mastectomy but no tumour was found in the breast. One of the patients received radiation therapy to the breast.

Adjuvant systemic treatment

One premenopausal patient (one positive node of 15) received systemic chemotherapy with five cycles of cyclophosphamide, methotrexate and 5-fluorouracil, and refused the sixth cycle. One postmenopausal patient received adjuvant treatment with tamoxifen.

Clinical and follow-up data were complete for all patients.

Results

The 15 women had a median age of 54 (range 36–72) years. All axillary masses contained adenocarcinoma and in seven patients this was poorly differentiated, consistent with a primary in the breast. Four patients had moderately well differentiated metastatic adenocarcinoma and four unclassified lesions.

Three patients died from recurrence at 16, 50 and 56 months after treatment of the axillary mass; one is alive at 42 months with recurrent disease of the liver and contralateral axilla. Two of these patients presented with supraclavicular node metastases. In two patients the tumour in the breast became detectable (clinically and mammographically) after 10 and 31 months of follow-up, but before other metastases. Treatment of these tumours consisted of simple mastectomy in one patient and lumpectomy with radiation therapy of the breast in the other.

Eleven patients have a median survival time of 92 (range 18–144) months without evidence of disease. In two of these contralateral breast carcinoma developed at 33 and 60 months; these cancers were treated by lumpectomy, axillary clearance and irradiation to the breast. The tumours were ductal cancers (not otherwise specified) with classification $pT_1 N_0$.

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Discussion

The frequency of occult breast carcinoma presenting with regional lymph node metastasis is difficult to determine but it may account for less than 0·45 per cent of primary operable breast cancer[1,3,9]. Apart from breast primaries many other adenocarcinomas may metastasize to axillary nodes[3,10], but in the absence of localized signs or symptoms there is little value in exhaustive evaluation attempting to find a primary tumour[1,3]. The present use of immunohistochemistry, oestrogen receptor analysis, cytogenetics and flow cytometry may strengthen the diagnosis of metastatic breast cancer[3,11], although a negative receptor result on lymph node biopsy does not rule out a breast primary.

Mastectomy with complete axillary clearance has been the recommended treatment for patients presenting with axillary lymph node metastases consistent with a breast primary[1-3]. Examination of the excised breast disclosed cancer in 8-82 per cent of patients[1,2,4,5,7,8]. Many of these patients, however, were treated at a time when mammography or localization biopsy may not have been available[1,4,7].

Two recent studies demonstrated that patients treated with radiotherapy to the breast have the same prognosis as those who undergo mastectomy[2,6]. In the present study the breast was left untreated in 14 of the 15 patients. At a median follow-up of 7·5 years carcinoma developed in the breast of two patients. This local failure rate is lower than those reported by Ellerbroek *et al.*[2] and Merson and colleagues[8] in comparable groups of patients, and even lower than the 19-27 per cent observed in patients treated with radiotherapy[2,6]. The progression-free survival rate of the whole of the present group was 73 per cent at a median follow-up of 7·5 years and survival thus seems not to be hampered by withholding immediate therapy to the breast. This is in concordance with the experience of others[2,8].

The availability of modern mammographic equipment allows the option of withholding definitive local therapy until clinical or radiographic appearance of the primary tumour. The axilla should preferably be treated by axillary clearance[12], although when supraclavicular node disease is present simultaneously the indication for axillary clearance is less convincing. The role of radiotherapy and adjuvant chemotherapy or hormonal therapy is to provide the same treatment for these patients as for those with a known breast primary and similar nodal stages. This means that at present all patients should receive systemic therapy with either combination chemotherapy or antihormone treatment[13].

Patients with axillary metastases histologically consistent with breast cancer should be treated identically to those with the same features and a proven breast primary. A 'wait and see' policy towards the breast may be warranted and an extensive search for an extramammary primary tumour in the absence of signs and symptoms is not useful.

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Concurrent hyperthyroidism and thyroid carcinoma

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Between 1986 and 1991, thyroidectomy was performed on 138 patients with hyperthyroidism. Thyroid carcinoma was found in eight patients (5·8 per cent). Eighty (58·0 per cent) of the 138 patients had toxic nodular goitre, 33 (23·9 per cent) toxic diffuse goitre and 25 (18·1 per cent) toxic adenoma. Concurrent carcinoma was more frequent in patients with toxic adenoma (8 per cent) than in those with Graves' disease (6 per cent) and toxic nodular goitre (5 per cent). Papillary carcinoma was found in seven patients and follicular carcinoma in one. Three papillary carcinomas were occult with a diameter less than 1·5 cm. Five patients received 100 mCi ^{131}I after operation. There was no morbidity. During follow-up of 10–45 months, there was neither death nor recurrence.

Thyroid carcinoma in patients with hyperthyroidism was first reported by Sokal[1] in 1954; it was observed that the incidence was 20-fold higher in those with thyrotoxicosis than the euthyroid state. Widely differing coincident frequencies (0·76–8·7 per cent) have been reported[1,2]. The possible coexistence of carcinoma, especially in patients with toxic nodular goitre, suggests that surgery is the preferred treatment[3]. In the present retrospective study, eight patients with concurrent hyperthyroidism and thyroid carcinoma were reviewed.

Patients and methods

Between 1986 and 1991, thyroidectomy was performed on 138 patients for hyperthyroidism. Eighty (58·0 per cent) had toxic nodular goitre, 33 (23·9 per cent) toxic diffuse goitre and 25 (18·1 per cent) toxic adenoma. Thyroid carcinoma was found in eight patients (5·8 per cent): four (5 per cent) with toxic nodular goitre, two (8 per cent) with toxic adenoma and two (6 per cent) with Graves' disease. During the same period, carcinoma was found in 66 (6·9 per cent) of 958 patients undergoing thyroidectomy.

The eight patients were seven women and one man of age 19–65 (mean 43·1) years. All patients were thyrotoxic at the initial clinical examination. Their symptoms and clinical features are summarized in *Table 1*. One patient had severe thyrotoxicosis associated with rapid enlargement of the gland. Laboratory investigation confirmed thyrotoxicosis in all patients. Clinical and radioisotope scan results are shown in *Table 2*. Propylthiouracil or methimazole was used before operation in all patients; the duration of therapy ranged from 3 to 12 months. None of the patients was suspected of having carcinoma before or during operation. Subtotal thyroidectomy was performed in six patients, near-total thyroidectomy in one and total thyroidectomy in one.

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Results

Of six patients in whom subtotal thyroidectomy was performed, three had occult papillary carcinoma. Of the remaining three patients, two were found to have papillary carcinoma and one follicular carcinoma. In these three patients ablation with radioactive iodine was used to eradicate the disease as the remnants were very small.

Follicular carcinoma was found in one patient with severe thyrotoxicosis associated with rapid enlargement of a goitre and a scan demonstrating a solitary hot nodule. The patient who underwent near-total thyroidectomy had papillary carcinoma confined to one lobe. Sclerosing papillary carcinoma was found in both lobes in the patient undergoing total thyroidectomy. In three patients with papillary carcinoma, histological localization of the tumour corresponded to areas

Table 1 *Details of patients*

Patient no.	Age (years)	Sex	History	Clinical examination
1	56	F	Slow enlargement of goitre for 4 years Symptoms of thyrotoxicosis for 1 year	Mild thyrotoxicosis; bilateral multinodular goitre
2	52	F	Slow enlargement of goitre for 3 years Symptoms of thyrotoxicosis for 1 year	Mild thyrotoxicosis; bilateral hyperplasia; nodule in left lobe
3	43	F	Slow enlargement of goitre for 25 years Symptoms of thyrotoxicosis for 1·5 years	Moderately thyrotoxic; bilateral multinodular goitre
4	40	F	Slow enlargement of goitre for 20 years Symptoms of thyrotoxicosis for 8 months	Mild thyrotoxicosis; bilateral hyperplasia; nodule in left lobe
5	65	F	Rapid enlargement of a nodule Symptoms of thyrotoxicosis for 1 year	Severe thyrotoxicosis; large nodule in right lobe
6	42	F	Slow enlargement of goitre for 17 years Symptoms of thyrotoxicosis for 3 months	Moderately thyrotoxic; one nodule in left lobe, one nodule in right lobe
7	19	F	Slow enlargement of goitre for 4 years Symptoms of thyrotoxicosis for 3 months	Moderately thyrotoxic; bilateral diffuse hyperplasia
8	28	M	Slow enlargement of goitre for 1 year Symptoms of thyrotoxicosis for 8 months	Moderately thyrotoxic; bilateral diffuse hyperplasia

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Table 2 *Radioisotope scan, operative and histological findings*

Patient no.	Radioisotope scan	Operative findings	Histological findings
1	Bilateral hyperplasia Areas of low uptake in both lobes	Bilateral hyperplasia Multiple small nodules in both lobes	Occult papillary carcinoma in left lobe
2	Bilateral hyperplasia Non-homogeneous uptake in both lobes	Bilateral hyperplasia Multiple small nodules in both lobes	Occult papillary carcinoma in right lobe
3	One cold nodule in right lobe Two cold nodules in left lobe	Cystic 10-cm nodule in right lobe Multiple small nodules in left lobe	Papillary carcinoma in right lobe
4	Bilateral hyperplasia Cold nodule in left lobe	Firm nodule in left lobe Frozen-section examination: adenomatous nodule	Papillary carcinoma in left lobe and partially in right lobe
5	Hot nodule in right lobe	Nodule of 5 cm in right lobe Multiple small nodules in left lobe	Follicular carcinoma in both lobes
6	Hot nodule in right lobe Irregular uptake in left lobe	Multiple nodules in both lobes	Occult papillary carcinoma in right lobe
7	High diffuse uptake	Bilateral diffuse hyperplasia	Papillary carcinoma in both lobes
8	High diffuse uptake	Bilateral diffuse hyperplasia	Two foci of papillary carcinoma in right lobe

of low uptake on a radioisotope scan. These results are summarized in *Table 2*.

At 4 weeks after surgery, a whole-body scan was performed in two patients and a thyroid scan in all eight. There was no evidence of local or distant metastasis. All patients were given oral thyroxine therapy. Patients received ablative doses of radioiodine, except for those with occult carcinoma.

Follow-up ranged from 10 to 45 (mean 30) months. There was no recurrence or death during this period.

Discussion

Different frequencies of concurrent hyperthyroidism and thyroid carcinoma have been reported[1–6]. The frequency of thyroid carcinoma in patients with Graves' disease was 2·5-fold greater than in those with toxic adenoma[7]. The carcinoma in patients with Graves' disease behaved more aggressively than that associated with toxic nodular goitre and toxic adenoma[7].

Based on data from 1848 patients with hyperthyroidism treated surgically, Rieger *et al.*[8] reported the incidence of coexisting malignancy as 0·76 per cent. It is remarkable that none of the 64 patients with Graves' disease had thyroid carcinoma. The authors concluded that the incidence of concurrent hyperthyroidism and malignancy was low in an endemic area of goitre. In contrast, the incidence of coexisting thyroid carcinoma and hyperthyroidism in the present study (5·8 per cent) was not much lower than that of carcinoma in euthyroid glands (6·9 per cent).

Thyroid-stimulating hormone (TSH) is thought to be the most important factor promoting growth and possibly genesis of thyroid carcinoma; differentiated thyroid carcinoma is known to contain TSH receptors. In rodents, TSH stimulation of the thyroid gland by goitrogenic diets leads to glandular hyperplasia and later neoplasia[9]. It is unclear whether human thyroid carcinoma results from excessive stimulation by TSH. Dobyns *et al.*[10] reported results of an analysis of 34 684 patients with hyperthyroidism treated with antithyroid drugs, ^{131}I, thyroidectomy, external radiation or a combination of these. The incidence of malignancy was higher in patients treated with drugs than in those receiving ^{131}I therapy or thyroidectomy and was associated with increased TSH levels.

The diagnosis of hyperthyroidism does not preclude concurrent thyroid carcinoma.

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Thyroid neoplasia coexistent with chronic lymphocytic thyroiditis

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During a 6-year period 115 patients presenting with thyroid enlargement had evidence of chronic lymphocytic thyroiditis on fine-needle aspiration cytology. Of 27 patients in whom histological analysis was carried out, 16 had neoplasms (follicular adenoma, four; follicular carcinoma, one; papillary carcinoma, four; lymphoma, seven). Assuming that neoplasia was not overlooked in the absence of histological examination, the overall incidence was 14 per cent and that of malignant disease 10 per cent. All patients with carcinoma had cytological features suspicious of neoplasia on the first or subsequent aspirates in addition to those of thyroiditis. Cytology was suspicious of lymphoma in only two of seven patients but increasing size of the thyroid swelling was a consistent feature. Evidence of chronic lymphocytic thyroiditis may lead to neoplasia being overlooked. Repeated cytological analysis is helpful in identifying coexistent carcinoma but unreliable in excluding lymphoma.

Chronic lymphocytic thyroiditis (Hashimoto's disease, autoimmune thyroiditis) is a common condition. In North-east Scotland (population 500000), approximately 140 patients with this diagnosis are registered annually on the Scottish Automated Follow Up Register.

The association of thyroid lymphoma with chronic lymphocytic thyroiditis is well known[1] but relatively rare. There is less awareness of the risk of other coexisting thyroid neoplasia. The typically firm or hard texture of isolated or diffuse chronic lymphocytic thyroiditis resembles that of thyroid carcinoma, but concomitant evidence of autoimmune disease (thyroid failure, raised autoantibody titre or cytological appearance) may influence the diagnosis to a degree that neoplasia is overlooked. The use of fine-needle aspiration cytology (FNAC) has heightened awareness of the frequency with which the two conditions may coexist.

Patients and methods

In the Grampian Region patients with thyroid swellings are usually referred to a joint medical–surgical thyroid clinic. Between January 1985 and December 1991, FNAC was in routine use and all patients with cytological evidence of chronic lymphocytic thyroiditis on one or more samples were studied retrospectively. Clinical characteristics, results of thyroid function tests (thyroxine, thyroid-stimulating hormone, free tri-iodothyronine), thyroid autoantibody levels, cytology, histology and management were reviewed.

Levels of thyroid autoantibodies (thyroglobulin antibody and thyroid microsomal antibody) were measured using a haemagglutination technique with a serial dilution method. Reactions at dilution levels of 1 in 100 or weaker were taken as positive.

FNAC was performed and interpreted as described previously[2]. A cytological diagnosis of chronic lymphocytic thyroiditis was based on the presence of a combination of lymphocytes, plasma cells and lymphoid follicle centre cells in association with thyroid follicular cells some or all of which showed oxyphil change (Askanazy cells, oncocytes).

The histology of all thyroid tissue removed was reviewed by a specialist pathologist.

Results

A total of 115 patients (five men, 110 women; mean age 51 (range 18–88) years) presented with thyroid enlargement and had cytological features consistent with chronic lymphocytic thyroiditis on at least one occasion. Clinically 34 patients had generalized thyroid enlargement, 60 a dominant swelling[3] within a generally enlarged gland and 21 isolated swellings. Thyroid autoantibody titres were raised in 73 patients and 44 had either clinical or biochemical evidence of thyroid failure. The combination of generalized thyroid enlargement, positive autoantibodies and thyroid failure was present in only 17 patients.

A group of 88 patients did not undergo surgery or large-bore needle biopsy and the diagnosis remained chronic lymphocytic thyroiditis.

Large-bore needle biopsy was carried out on two patients with suspected lymphoma and 25 underwent surgery. Of these 27 patients, 16 had neoplasms: follicular adenoma, four; follicular carcinoma, one; papillary carcinoma, four; and lymphoma, seven.

In 15 patients the indication for operation or large-bore needle biopsy was a combination of clinical suspicion of neoplasia with additional suspicious findings on cytology. In seven of these patients suspicion of neoplasia was raised on the first aspirate (histological findings were: papillary carcinoma, three; oxyphil follicular carcinoma, one; follicular adenoma, one; lymphoma, one; and colloid degeneration, one) and in eight patients a subsequent aspirate was reported as possibly neoplastic (histology: papillary carcinoma, one; follicular adenoma, one; lymphoma, one; and colloid degeneration, five).

Nine patients underwent operation because of clinical suspicion alone. Despite cytological evidence of chronic lymphocytic thyroiditis the isolated or dominant nature of the thyroid swelling was suspicious in four patients, two of whom proved to have follicular adenoma. Increasing size of the gland was suspicious in five patients; all proved to have lymphoma.

Of the remaining three patients, one had a dominant swelling causing tracheal compression. Cytological findings were consistent with lymphocytic thyroiditis but histology showed colloid degeneration. Two patients had a dominant swelling removed (patient preference) when there was no clinical suspicion of neoplasm; lymphocytic thyroiditis was confirmed histologically in both.

Six of the seven patients with thyroid lymphoma were women and all seven were aged more than 50 years. Apparent increase in size of the thyroid swelling, often rapid, was a consistent feature, and in five patients there was clinical and radiological evidence of tracheal compression. Results of cytology were diagnostic in one and suspicious of neoplasia in another. Histology was obtained by large-bore needle biopsy in two patients and the thyroid isthmus was resected in five

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because of clinical suspicion together with tracheal compression. The histological features in these seven patients were of B cell centroblastic non-Hodgkin's lymphoma.

Discussion

Assuming that neoplasia had not been overlooked in the absence of histological analysis, 16 (13·9 per cent) of 115 patients with thyroid swelling and cytological evidence of chronic lymphocytic thyroiditis had neoplastic disease and 12 (10·4 per cent) had malignancy. The problem of neoplasia coexistent with lymphocytic thyroiditis is therefore clinically significant. The incidence in the present report is higher than commonly recorded[4,5] and reflects selection bias in a specialist clinic.

Identifying all patients with chronic lymphocytic thyroiditis is difficult because the diagnosis rests on a number of variably present factors. The classical clinical features of a hard bosselated goitre, thyroid failure and raised autoantibody titres were found in only 15 per cent of the present patients. There is also a significant incidence of raised autoantibody titres in the general population[6]. Furthermore, lymphocytic infiltration of the thyroid in asymptomatic patients[7] is common and autoantibody-negative chronic lymphocytic thyroiditis may be more prevalent than previously thought[8].

This study highlights two potential diagnostic pitfalls: the patient who has carcinoma despite evidence of chronic lymphocytic thyroiditis and the patient with coexistent lymphoma. All the patients with carcinoma or follicular adenoma presented with an isolated or dominant swelling and in all those with carcinoma cytology was reported as possibly neoplastic, in four of five cases on the first sample. Oxyphil tumours are difficult to distinguish from chronic lymphocytic thyroiditis[9] but the one such patient in the present series was identified by FNAC. Provided that clinical suspicion, despite evidence of lymphocytic thyroiditis, is maintained and cytological analysis is routine, these patients should be identified although repeated sampling is necessary.

Patients with coexisting lymphoma are more difficult to diagnose[5]. In the present study the only consistent clinical feature was increasing size of the gland, often rapid and usually associated with tracheal compression. Willems and Lowhagen[10] stated that lymphoma may be distinguished from chronic lymphocytic thyroiditis on cytology but, as described by Suen and Quenville[11], the present series demonstrated difficulties. The accuracy of FNAC in identifying lymphoma improves with experience but the method is less reliable than large-bore needle biopsy[5]. The latter may give sufficient information for the diagnosis and classification of lymphoma. The need for adequate tissue for histological classification and the frequency of tracheal compression suggest that isthmusectomy may be a diagnostic and therapeutic procedure.

Evidence of chronic lymphocytic thyroiditis in a patient with thyroid enlargement should not lead to diagnostic complacency. FNAC with repeated sampling is helpful in detecting coexistent carcinoma but unreliable in excluding lymphoma. Clinical awareness of the possibility of neoplasia is critical, particularly in detecting lymphoma.

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Oesophagogastrectomy for carcinoma of the oesophagus and cardia

A retrospective review was undertaken of all oesophagectomies performed within a single unit over a 12-year period. In all, 298 patients with primary oesophageal cancer underwent resection between March 1979 and December 1991. Four patients had a three-stage oesophagogastrectomy, 27 a thoracoabdominal oesophagogastrectomy and 267 a Lewis procedure. Dysphagia was the predominant presenting symptom. The duration of symptoms was not related to the stage of disease. Before diagnosis, 52 per cent of patients tolerated symptoms for 2–4 months. Adenocarcinoma was found in 180 tumours and squamous cell carcinoma in 103. Half the patients had evidence of metastatic spread at the time of laparotomy or thoracotomy. The 30-day mortality rate was 10 per cent and the overall actuarial 5-year survival rate of all patients 23 per cent. The actuarial 5-year survival rate of patients without lymph node involvement was 39 per cent compared with 17 per cent for those with positive nodes ($P < 0.05$*). Five of eight patients who had anastomotic leakage died. The almost unselected nature of this series, coupled with the favourable results of oesophagectomy, support the contention that resection remains the preferred mode of treatment for carcinoma of the oesophagus of all histological types.*

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The incidence of oesophageal carcinoma is increasing in Britain[1]; this holds for both adenocarcinoma and squamous cell carcinoma[2]. However, adenocarcinoma appears to contribute a higher proportion of cancers in the UK than in most series reported from overseas[3,4]. Surgical treatment of oesophageal carcinoma in 1980 had a dismal 5-year survival rate of 4 per cent[5]. However, improved survival rates have been reported over the past decade by a number of centres[6–9]. This study reports experience with oesophagogastrectomy for carcinoma of the oesophagus performed by one surgeon in a district general hospital.

Patients and methods

A retrospective review was undertaken of all oesophagectomies performed within the Thoracic Unit at Derriford Hospital, Plymouth. In all, 298 patients with primary oesophageal carcinoma underwent resection during the period March 1979 to December 1991. This is the sole unit serving a population of 400 000–450 000, so this series is unselected. The number of oesophageal resections at this institution has increased over the years (*Figure 1*); there were 36 in 1991.

Preoperative assessment included chest radiography, abdominal ultrasonography, upper gastrointestinal endoscopy, bronchoscopy and computed tomography (CT). Resectability was assessed at laparotomy or thoracotomy and resection felt to be contraindicated if widespread infiltration of adjacent organs, or diffuse pleural or peritoneal carcinomatosis was found. Staging of oesophageal cancer was performed according to the American Joint Committee on Cancer guidelines[10]. Stage I disease was defined as tumour invading the mucosa or submucosa but not the muscularis, with no nodal or metastatic involvement. Stage II disease was limited to the oesophagus. Stage III disease included transmural involvement or lymph node metastasis (N_{0-2}). Stage IV indicated direct tumour extension to the diaphragm or pericardium, or more distant visceral metastases. Chemotherapy and radiotherapy were not given before surgery but were used occasionally after operation for palliation of recurrent or residual disease.

A variety of surgical procedures were performed depending on the location of the primary tumour. If the lesion was in the upper third of the thorax, three-stage oesophagogastrectomy was performed as advocated by McKeown[11]. Lesions of the middle and lower oesophagus were resected using a Lewis[12] procedure. In this, the most common operation in the series, end-to-side anastomosis of the oesophagus to the posterior wall of the stomach was performed using a circular stapler (Auto Suture, Ascot, UK)[13]. The contiguous thoracoabdominal approach was also used in some patients.

Statistical analysis

Survival was estimated using the method of Kaplan and Meier[14]. The difference between groups was assessed by the log rank test[15,16]. The 5-year survival rates include operative deaths.

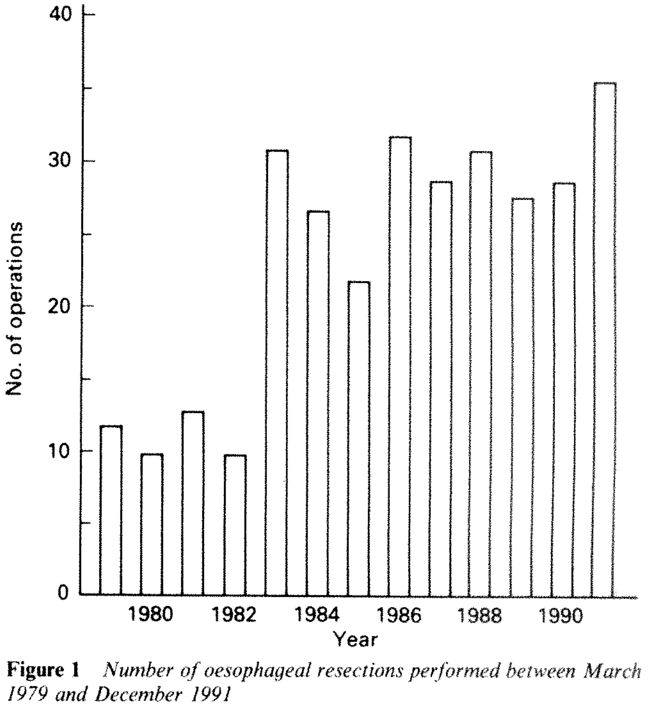

Figure 1 *Number of oesophageal resections performed between March 1979 and December 1991*

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Results

A total of 216 men and 82 women aged 34–87 years underwent oesophageal resection, a male:female ratio of 2·6:1. The age distribution for all patients with oesophageal cancer obtained from the regional cancer registry was similar to that of those who had undergone oesophageal resection (*Figure 2*).

Of the 298 patients, 267 underwent a Lewis procedure, four three-stage oesophagogastrectomy and 27 thoraco-abdominal oesophagogastrectomy.

Dysphagia, weight loss and retrosternal or epigastric pain were the presenting symptoms in most patients either in combination or alone (*Table 1*). Dysphagia was the predominant symptom in 255 patients (86 per cent) and in 38 (13 per cent) was the sole complaint. Haematemesis was the presenting feature in four men and oesophageal malignancy was found in one patient during the course of investigations for chronic anaemia. In all, 52 per cent of patients tolerated symptoms for 2–4 months before the diagnosis was made. The duration of symptoms was not related to the stage of disease. For example, of 22 patients who had symptoms for 11–12 months, ten had localized tumours (N_0M_0) and only three had distant metastases, and of 50 patients with symptoms for 1–2 months, 32 had nodal involvement.

Adenocarcinoma was the predominant histological type. Histological analysis (*Table 2*) revealed that 103 tumours were squamous cell carcinoma and 180 adenocarcinoma. Most adenocarcinomas were presumed to be gastric in origin but in 21 patients (12 per cent) such tumours were found to arise in a columnar epithelium-lined (Barrett's) oesophagus. Interestingly, adenocarcinoma was the predominant tumour in men (73 per cent) while squamous cell carcinoma predominated in women (67 per cent). In addition, anaplastic carcinoma was found in 13 patients (4 per cent). One patient had a mixed lesion and another a tumour that proved impossible to define histologically.

Half the patients had evidence of metastatic spread at the time of surgery. Staging of the resected specimen in conjunction with the findings at operation revealed the numbers of patients with stage I, II, III and IV disease to be seven, 110, 142 and 39 respectively. For those with stage III disease, lymph nodes lying along the left gastric artery were the most commonly involved. Despite preoperative assessment with ultrasonography and CT, disease was frequently found to be more extensive than had been anticipated (*Table 3*). The operative mortality rate, defined as death within 30 days, was 10 per cent. Postoperative complications are given in *Table 4*.

There were eight anastomotic leaks (3 per cent); five of these patients died. Of the 298 patients, 66 (22 per cent) developed

Table 1 *Presenting symptoms*

	Men (n = 216)	Women (n = 82)	Total (n = 298)
Dysphagia	181 (61)	74 (25)	255 (86)
Weight loss	145 (49)	58 (19)	203 (68)
Pain on swallowing	67 (22)	29 (10)	96 (32)
All three of the above	48 (16)	19 (6)	67 (22)
Dysphagia alone	28 (9)	10 (3)	38 (13)
Weight loss alone	2 (1)	1 (0)	3 (1)
Pain alone	5 (2)	2 (1)	7 (2)
Haematemesis	4 (1)	0 (0)	4 (1)
Anaemia	1 (0)	0 (0)	1 (0)

Values in parentheses are percentages

Table 2 *Histopathological diagnosis*

	Men	Women	Total
Squamous cell carcinoma			
Well differentiated	20	14	34
Moderately differentiated	14	22	36
Poorly differentiated	14	19	33
Total	48 (22)	55 (67)	103 (35)
Adenocarcinoma			
Well differentiated	44	4	48
Moderately differentiated	37	6	43
Poorly differentiated	77	12	89
Total	158 (73)	22 (27)	180 (60)
Anaplastic	8	5	13 (4)
Mixed	1	0	1 (0)
Unestablished	1	0	1 (0)
Total	216	82	298 (100)

Values in parentheses are percentages

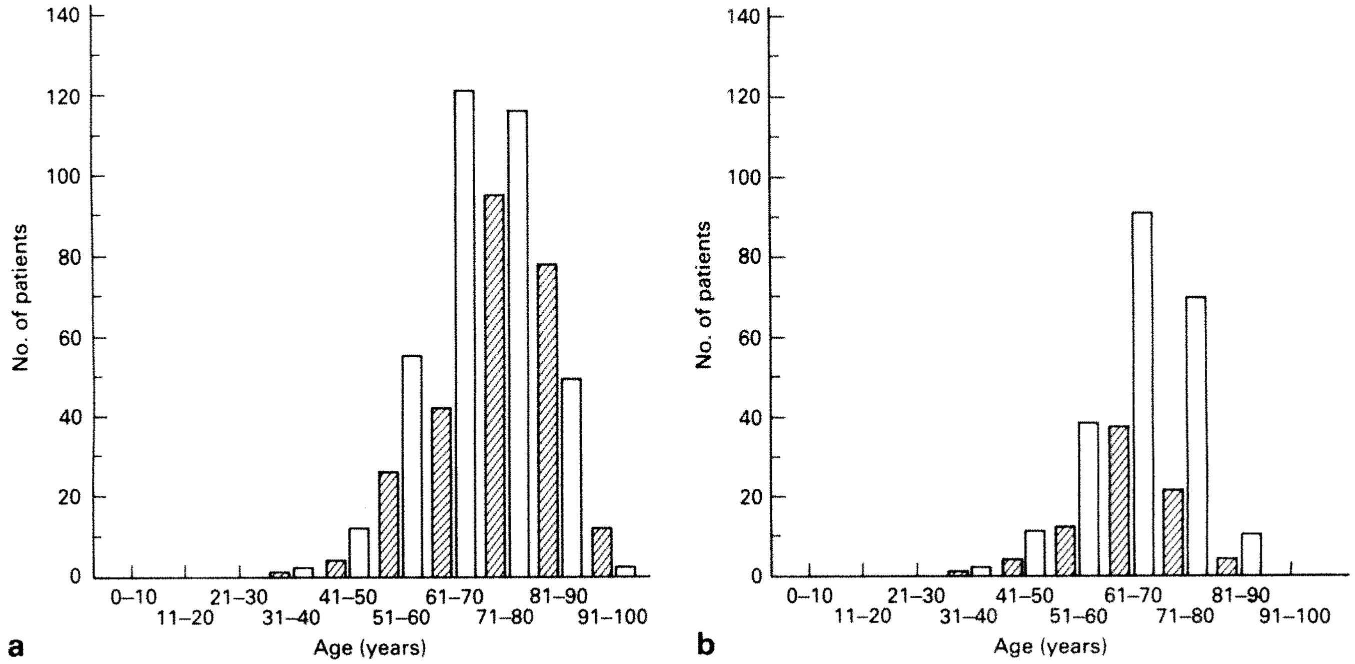


Figure 2 *Age distribution of incidence of oesophageal carcinoma in male* (□) *and female* (▨) *patients* **a** *in the South-western Region (courtesy of the Bristol Cancer Registry) and* **b** *who underwent resection in the present series*

Table 3 *Lymph node involvement and distant metastasis*

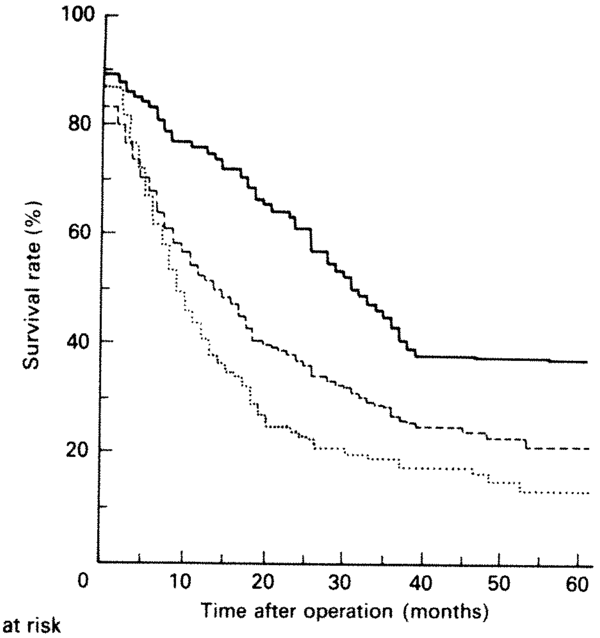
	Men	Women	Total
Lymph nodes			
Gastric	92	57	149 (50)
Coeliac	70	29	99 (33)
Mediastinal	24	14	38 (13)
Supraclavicular	1	1	2 (1)
Metastases			
Liver	8	4	12 (4)
Pancreas	7	3	10 (3)
Diaphragm	6	3	9 (3)
Lung	4	2	6 (2)
Tracheobronchial	8	3	11 (4)
Aorta	4	1	5 (2)
Pericardium	1	2	3 (1)

Values in parentheses are percentages

Table 4 *Postoperative morbidity*

	No. of patients
Anastomotic leakage	8 (5)
Anastomotic stricture	66
Pulmonary problems	43 (9)
Cardiovascular problems	38 (13)
Recurrent laryngeal nerve damage	2
Gastric tube stasis	1
Pulmonary embolism	7 (2)
Pancreatic fistula	1
Dumping	10
Postvagotomy diarrhoea	16
Subphrenic abscess	3
Haemorrhage	5
Wound infection	29

Values in parentheses are numbers of hospital deaths



No. at risk													
Total	298	233	173	139	114	97	80	68	57	32	29	26	26
Node-positive	181	135	92	67	49	41	33	27	25	22	19	17	17
Node-negative	117	98	81	72	65	56	47	41	32	10	9	9	9

Figure 3 *Cumulative survival curves for all patients who underwent resection (-----), those with positive nodes (·····) and those without nodal involvement (——). Operative deaths were included; there was a significant difference between the group with nodal involvement compared with that without (P < 0·05)*

anastomotic stricture requiring dilatation. The size of stapler used was 25 mm in 58 of these 66 patients; a 28-mm stapler was used for the remaining eight. The majority of anastomotic strictures occurred within 6 months of operation.

The drainage procedure was pyloroplasty in 223 patients (75 per cent) and pyloromyotomy in 50 (17 per cent). No drainage procedure was undertaken in 25 patients (8 per cent); one patient developed gastric outlet obstruction and underwent pyloroplasty 21 days after operation.

Survival

The overall actuarial 5-year survival rate of all patients is shown in *Figure 3*. Survival rates at 1, 2, 3, 4 and 5 years were 54, 39, 29, 25 and 23 per cent.

The 5-year survival rate for patients without lymph node involvement was 39 per cent while the corresponding figure was 17 per cent for the node-positive group. This difference in survival was significant ($P < 0{\cdot}05$). The actuarial 5-year survival rate for patients with stage IV disease was 15 per cent.

Discussion

A threefold increase was recorded in the number of oesophageal resections performed in this unit in 1983 compared with previous years. The reason for this is not clear but it may reflect a change in referral pattern. The main source of referrals was initially from other departments within the hospital but, as the unit became established, general practitioners referred patients directly.

The age distribution of the overall incidence of oesophageal carcinoma matches reasonably well that of the present patients who had undergone resection (*Figure 2*). This finding suggests that there was little selection of patients on the grounds of age. Patients of all ages were operated on as the biological age was considered more important than chronological age. The authors rarely used non-resectional techniques such as intubation for the palliation of malignant dysphagia.

The type of procedure used in the present series is generally considered 'palliative' even though the resection may be radical in extent. *En bloc* procedures were not used. The main aim of therapy was to restore swallowing.

Matthews *et al.*[17] compared the results of oesophageal resection undertaken by 127 surgeons who operated occasionally (averaging three or fewer resections per annum) with those of four surgeons who operated more frequently (averaging six or more resections annually). The operative and 5-year mortality rates were significantly lower in the second group. The low mortality and morbidity rates in the present series support the view that oesophagogastrectomy should be carried out by surgeons who perform this procedure frequently.

The duration of symptoms before oesophagectomy bore no relationship to the stage of disease at operation, in agreement with previous reports[18,19]. The findings indicate that spread of disease may occur without overt symptoms of dysphagia, weight loss, retrosternal pain or difficulty swallowing.

In 1990, Muller *et al.*[20] reviewed 1201 papers on oesophageal carcinoma published between 1980 and 1988; they found a mean 5-year survival rate of 20 per cent. In series containing both squamous carcinoma and adenocarcinoma, the mean 5-year survival rate was lower than in those that included only squamous cell carcinoma (18 *versus* 24 per cent). The 5-year survival rate of 23 per cent in the present series thus compares favourably with those published.

Barrett's oesophagus (columnar-lined oesophagus) has been recognized as a premalignant condition. Haggitt *et al.*[21] reported that 12 of 14 patients with oesophageal adenocarcinoma had associated Barrett's oesophagus. More recently, Hamilton *et al.*[22] found that 64 per cent of oesophagogastrectomy specimens with adenocarcinoma were from patients with Barrett's oesophagus. They emphasized that there is under-reporting of carcinoma associated with Barrett's oesophagus;

only 38 per cent of patients in their series were recognized on preoperative endoscopy and biopsy to have this association. The prevalence of Barrett's oesophagus was 12 per cent in the present series. The resection specimens were, however, not subjected to extensive histopathological examination and the prevalence of adenocarcinoma arising in Barrett's oesophagus was probably under-reported.

The importance of nodal involvement in prognosis was demonstrated by the lower 5-year survival rate for patients with compared with those without nodal involvement (17 *versus* 39 per cent). Survival was adversely affected by positive regional lymph nodes ($P < 0{\cdot}05$) and distant lymphatic metastases ($P < 0{\cdot}05$).

Postlethwait and Durham[23] reported an anastomotic leakage rate of 36 per cent in a series of 512 operations. The use of staplers for oesophageal anastomosis had made this step of the procedure much safer, leakage rates of 0–3·5 per cent being reported[12,23–25]. In the present series there was a 3 per cent incidence of anastomotic leakage, but the seriousness of this complication is shown by the fact that five of the eight patients in whom the anastomosis leaked died. Anastomotic leakage was more common after extensive gastric resection; this may have been a result of the shorter gastric tube, leading to tension at the anastomosis[26]. One patient in the present series underwent choledochoduodenostomy for common bile duct stones at the time of oesophageal resection; this may have contributed to leakage by creating tension at the anastomosis. The authors now advocate that bile duct stones be dealt with endoscopically either before or after oesophagectomy. It is important that the duodenum is thoroughly mobilized. The range of methods described to protect the oesophagogastric anastomosis indicates that there is no guaranteed way of guarding against dehiscence of an intrathoracic anastomosis. Polyglactin 910 mesh graft, lung tissue, visceral pleural patch, omentum, peritoneum, pericardium, oesophageal muscular cuffs, intercostal pedicle and gastric fundus patch have all been used for the protection of the oesophagogastrostomy[27–29]. Reinforcing sutures were used in the present series to 'inkwell' the stapled anastomosis. The initial management of anastomotic leakage was total parenteral nutrition, complete fasting, intrathoracic drainage and antibiotics, but nevertheless five of the eight patients died.

Anastomotic stricture developed in 22 per cent of patients in this series. While this is a high rate, it is comparable to that in other series using the EEA stapler[30]. The use of a small stapler (25 mm) and of reinforcing sutures to 'inkwell' the stapled anastomosis may be contributory factors. The choice of stapler was made after 'sizing' the diameter of the transected oesophagus with metal rods. In each case the largest possible stapler was used but this was, of course, dependent on the luminal width of the oesophagus. Injudicious forcing of the detached stapler head into the lumen of the transected oesophagus may result in splitting of the oesophageal wall and is to be discouraged. There may be a trade-off between the risk of anastomotic stricture using reinforcing sutures and the risk of anastomotic leakage. Dilatation of a stricture was felt preferable to the dire consequences of anastomotic leakage. Most of the anastomotic strictures presented within 6 months of operation. Only patients who complained of dysphagia were investigated.

Pyloroplasty was the drainage procedure most commonly performed, although pyloromyotomy was used in 17 per cent of patients. After pyloromyotomy, any inadvertent breach of the mucosal surface was tested with insufflation of air via a nasogastric tube. Not infrequently, however, the oesophageal tumour prevented passage of the nasogastric tube. Pyloroplasty was then performed in preference to pyloromyotomy. Dark *et al.*[31] reported that pyloroplasty was not used in a series of 449 resections. Six patients developed inadequate gastric emptying, requiring pyloroplasty. Mannell *et al.*[32] evaluated the role of pyloroplasty in the retrosternal stomach in a randomized controlled trial and found that nine of 20 patients in whom the pylorus was left intact had gastric tube stasis. The present authors now routinely perform pyloroplasty or pyloromyotomy and have not observed gastric stasis.

The 30-day mortality rate after resection was 10 per cent in the present series. This rate is similar to those in other series, especially bearing in mind the elderly population (77 per cent of patients were over 60 years old).

Intubation has been used as the primary method of treatment in many 'medical' centres in the UK. The almost unselected nature of the present series, coupled with the favourable results of resection, argue against such a policy. Intubation was rarely used. Oesophageal resection provides good results in the palliation of malignant dysphagia and is the treatment of choice in patients fit to undergo surgery. As in other series[33], adenocarcinoma was found in 60 per cent of patients. It is generally accepted that surgery is the best treatment, although radiotherapy has been advocated as an alternative for squamous cell carcinoma. However, the available evidence[34–36] indicates poor survival rates of between 5 and 10 per cent using this treatment. It is our contention that resection remains the preferred mode of treatment for carcinoma of the oesophagus of all histological types and that resection can be accomplished with acceptable morbidity and mortality rates. Furthermore, there is a reasonable long-term outlook for those with favourable stages of the disease.

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Non-operative treatment of small bowel obstruction following appendicectomy or operation on the ovary or tube

This study examined the hypothesis that small bowel obstruction in patients whose only previous laparotomy was for appendicectomy or operation on the ovary or tube is unlikely to resolve with non-operative management. Results of 330 admissions for small bowel obstruction were examined. In 40 cases the only previous laparotomy was at appendicectomy or tubo-ovarian operation; in 38 (95 per cent) of these division of adhesions was undertaken compared with 154 (53 per cent) of the remaining 290 ($P < 0\cdot00001$). In the former group band adhesions were commoner (86 versus *45 per cent, $P < 0\cdot00001$), bowel resection was required more frequently (22* versus *10 per cent, $P = 0\cdot02$) and it was considered safe to give a trial of non-operative management less often (60* versus *85 per cent, $P = 0\cdot0004$). A trial of conservative management may be unsafe or not worth while in patients with obstruction following earlier appendicectomy or operation on the ovary or tube.*

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In 1933 successful treatment of small bowel obstruction was reported in which some patients received nasoenteric suction and intravenous fluid therapy[1]. It was concluded:

> 'Only after this method of treating acute mechanical obstruction has been tried in the hands of many practitioners under varying circumstances will its limitations and possibilities become well defined.'

Numerous attempts have been made to predict which patients can be treated successfully with non-operative management. Continuous abdominal pain, localized pain, peritonism, tachycardia, high temperature, leucocytosis, high levels of amylase and lactic dehydrogenase, and clinical judgement have been analysed alone and in combination, in retrospective and prospective trials[2–12]. Their predictive power has been found to be disappointingly low.

Of patients presenting with small bowel obstruction caused by adhesions, 27–83 per cent are given a trial of non-operative treatment[10–14]. Between 22 and 52 per cent of these will eventually undergo laparotomy and 5–14 per cent require bowel resection for ischaemia[10–13]. When resection is needed the mortality rate can be 15–20 per cent[10,11,13].

It has been the authors' observation that, of patients presenting with small bowel obstruction, it is most uncommon for obstruction in those whose only previous laparotomy was for appendicectomy or operation on the ovary or tube to settle with non-operative management. When laparotomy is undertaken in such patients, a closed loop of bowel is typically found to be caught by a band adhesion. This type of obstruction is highly unlikely to settle without operative intervention and prolonged observation may lead to bowel ischaemia. This study was undertaken to evaluate the validity of this observation.

Patients and methods

A computerized coding system in use since 1986 identified patients with small bowel obstruction in the 6-year period 1986–1991. Patients who developed small bowel obstruction in hospital after a laparotomy and those with an obstructed external hernia were excluded. Patients with small bowel obstruction from specific causes were excluded (carcinoma in 18, radiation enteritis in nine, intra-abdominal abscess in six, Crohn's disease in three, anastomotic narrowing in one). Three sets of admission notes were studied (from the emergency department resident, the surgical registrar and the team intern), ensuring that collection of data was as reliable as possible. In five patients the nature of the previous laparotomy was unclear after reviewing the admission, original hospital and local doctor's notes, and operative findings. These were recorded as 'laparotomy (other)'.

Statistical analysis was by Fisher's exact test and two-tailed P values are given.

Results

There were 330 admissions: 127 of male patients and 203 female. The mean age was 59 (range 16–96) years. There were 260 patients in the study as 44 were admitted more than once.

In 34 cases the previous major laparotomy was for appendicectomy, through a grid-iron incision in all. In 31 this was the only procedure whereas in three cases operations on the ovary or tube had been performed. In 32 of the 34 cases division of adhesions was required while in only two was non-operative management successful. In the remaining 296 cases in the study, division of adhesions was necessary in 160 and obstruction settled with conservative management in 136. The difference between the two groups was highly significant ($P < 0\cdot00001$).

In six patients the only previous operation was on the ovary or tube: tubal ligation in three, salpingectomy in one, ovarian cystectomy in one and removal of an ectopic pregnancy followed later by a tubal ligation in one. In all six cases division of adhesions was required compared with 186 in the other 324 cases ($P = 0\cdot04$). The three patients in the appendicectomy group who had also undergone tubo-ovarian operations all required division of adhesions.

Data for the 40 cases of obstruction following appendicectomy and/or tubo-ovarian operation are summarized in *Table 1*. In this group band adhesions were the cause of obstruction in 32 of the 37 cases in which the type of adhesion was noted in the operative report, compared with 62 of 139 such cases in the remainder of the study ($P < 0\cdot00001$). Bowel

Table 1 *Outcome according to previous operation*

Previous operation	Division of adhesions	Successful conservative treatment
Appendicectomy and/or tubo-ovarian operation	38	2
Other	154	136

$P < 0\cdot00001$ (Fisher's exact test)

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Table 2 *Outcome according to number of previous laparotomies*

No. of previous laparotomies	No. of cases	Division of adhesions
0	9	9 (100)
1	128	90 (70)
2	92	47 (51)
3	41	22 (54)
4	34	17 (50)
≥5	26	7 (27)
Total	330	192 (58)

Values in parentheses are percentages

Table 3 *Outcome according to previous operation in patients who had undergone only one laparotomy*

Previous laparotomy	No. of cases	Division of adhesions
Appendicectomy	31	29 (94)
Tubo-ovarian operation	5	5 (100)
Large bowel operation	32	12 (38)
Hysterectomy	17	12 (71)
Gastric operation	9	5 (56)
Other	34	27 (79)
Total	128	90 (70)

Values in parentheses are percentages. Groups other than tubo-ovarian with fewer than nine cases are included in 'Other'

resection for ischaemia was required in nine of the combined group compared with 28 of the other 290 cases ($P = 0{\cdot}02$). Seven of the nine bowel resections in the former group were in patients initially receiving non-operative treatment. It was considered safe to undertake a trial of non-operative management in 24 of the 40 combined cases, compared with 247 of the remaining 290 ($P = 0{\cdot}0004$).

In *Table 2* outcome is presented according to the number of previous laparotomies. In nine cases patients had not undergone a previous laparotomy; in five a trial of non-operative management was undertaken. In all nine cases division of adhesions proved necessary, compared with 183 of the remaining 321 cases ($P = 0{\cdot}01$). This group followed a similar pattern to patients who had had an appendicectomy and/or tubo-ovarian operation, as all nine had band adhesions and three required bowel resection for ischaemia. In *Table 3* the outcome of those who had undergone only one previous laparotomy is summarized.

In the 330 admissions, bowel resection for ischaemia was required in 37, in which 28 patients were initially managed non-operatively, with a mean delay from presentation to laparotomy of 34 (range 4–96) h. There were 13 deaths, 12 of which occurred in patients initially given non-operative treatment. Four did not have a laparotomy before death; of the nine who did, five required bowel resection, one of whom had had only an appendicectomy. The overall mortality rate was 4 per cent, rising to 14 per cent in those who required bowel resection.

Discussion

Of patients presenting with small bowel obstruction, it is unlikely for obstruction in those whose only previous laparotomy was for appendicectomy or tubo-ovarian operation to settle with non-operative management. This group was distinctive in other ways: band adhesions were found more frequently and bowel resection for ischaemia required more often. It was considered safe to give a trial of non-operative management less often. This group probably lies at one end of a spectrum and the outcome of episodes of adhesional small bowel obstruction is determined, in part, by the number and type of previous laparotomies. Band adhesions appear to be a major influence on outcome.

The finding that patients who had undergone appendicectomy and/or tubo-ovarian operation had a trial of non-operative management less often than others may reflect sound clinical judgement. There is a tendency, however, to offer non-operative treatment to patients who have had multiple previous laparotomies. Surgeons may be concerned that very dense adhesions will result in a prolonged and hazardous operation. Ellis[15] has suggested that patients who have undergone multiple difficult laparotomies for lysis of adhesions may have intestinal loops so matted that they are unlikely to become strangulated. This tendency may be responsible for some of the difference in the laparotomy rate between those who have had one previous laparotomy and those who have had multiple procedures. The present study has identified a group of patients, who could be identified on admission, who eventually underwent division of adhesions in 95 per cent of cases.

These findings may be relevant only to similar populations with similar standards of healthcare. The state of the appendix at appendicectomy may be a determinant of band adhesion formation and patients with bowel obstruction may initially be managed in smaller hospitals and referred only if they require operative management.

Immediate laparoscopic division of adhesions may be a particularly suitable form of management in this group of patients and may reduce the number of bowel resections required. Adhesion formation might be reduced by the application of recombinant tissue plasminogen activator[16]. One early report suggests that laparoscopic appendicectomy is associated with less adhesion formation[17].

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Reduction in circulating levels of CD4-positive lymphocytes in acute pancreatitis: relationship to endotoxin, interleukin 6 and disease severity

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The proportion of peripheral blood mononuclear cells expressing the T helper cell phenotype and levels of antiendotoxin core antibody, interleukin (IL) 6 and C-reactive protein (CRP) were determined within 48 h of admission in a group of 29 patients with acute pancreatitis (16 mild, 13 severe attacks). There was a significant decrease in the proportion of T helper cells (12·2 versus *34·9 per cent,* $P < 0{\cdot}01$*) and significant increases in levels of IL-6 (69·5* versus *< 10 pg/ml,* $P < 0{\cdot}01$*) and CRP (119* versus *30·5 mg/l,* $P < 0{\cdot}01$*) in severe compared with mild attacks. During the convalescent stage at 3 months after admission, severe attacks were characterized by a significant increase in the proportion of T helper cells compared with the acute period (22·4* versus *10·6 per cent,* $P < 0{\cdot}01$*). A persistently low proportion of T helper cells was associated with residual pancreatic necrosis. The presence of circulating endotoxin was demonstrated in two mild and two severe attacks using the* Limulus *amoebocyte lysate assay, and abnormal levels of antiendotoxin core antibodies were found in 70 and 92 per cent of mild and severe attacks respectively. There was a strong inverse correlation between levels of CRP and the proportion of T helper cells in severe disease (*$r = -0{\cdot}76$*,* $P = 0{\cdot}004$*). Translocation of endotoxin from the gastrointestinal tract may partly explain the abnormal levels of T helper cells, IL-6 and CRP.*

After a severe attack of acute pancreatitis sepsis is now the leading cause of death[1]. Abnormalities in immune function such as a decreased proportion of T helper lymphocytes in the population of peripheral blood mononuclear cells[2], lowered production[3,4] of interleukin (IL) 2, decreased T cell proliferation[2] and increased prostaglandin E_2 production by monocytes[5] occur in patients with burns and trauma and correlate with the incidence of sepsis and outcome. A decrease in delayed-type skin hypersensitivity is common to patients with burn injury, blunt trauma[6] and acute pancreatitis[7], but the extent of other abnormalities of immune function in pancreatitis remains unclear.

Suppression of cellular immune function may result in part from exposure to bacterial endotoxin, a constituent of the Gram-negative bacterial outer membrane that comprises a lipid A–oligosaccharide core and a polysaccharide side chain. In addition to its role in the 'sepsis syndrome'[8], exposure to endotoxin may reduce the proportion of T helper cells in peripheral blood[9]. Endotoxin probably exerts many of its actions via cytokines that are released from monocytes[10–12]; these include IL-6, which is involved in B and T cell maturation, and is a reliable indicator of sepsis[13].

Previous studies have demonstrated that endotoxaemia is common in severe acute pancreatitis[14,15]. Reduced levels of CD4-positive cells (T helper lymphocytes) may be found in such patients in addition to other markers of recent endotoxin exposure, and these abnormalities may provide a potential target for immunomodulatory therapy. To overcome the difficulties associated with detection of endotoxin by the *Limulus* amoebocyte lysate test[16], assays for the measurement of circulating endogenous antiendotoxin core antibodies have been developed[17,18]. In the present study, levels of endotoxin, antiendotoxin core antibody, IL-6, C-reactive protein (CRP) and circulating T helper cells were measured in 29 patients with acute pancreatitis.

Patients and methods

Patients

Criteria for the diagnosis of acute pancreatitis were acute abdominal pain associated with a plasma amylase level >1000 units/l and a consistent clinical course. Attacks were classified as mild or severe; a severe attack was defined as a fatal outcome or the development of pancreatic necrosis, abscess or pseudocyst. Patients were cared for in a number of different hospitals but all were reviewed regularly by one author (P.J.C.) until discharge from hospital.

One patient underwent surgical pancreatic debridement and the remainder were treated conservatively with intravenous fluids, parenteral nutrition and antibiotics as indicated clinically. Venous blood was collected within 48 h of admission.

Normal proportions of T helper cells in peripheral blood mononuclear cell preparations were determined for 11 healthy controls. T helper cell proportions were also determined in eight patients with mild and six with severe pancreatitis 3 months after the acute attack.

Methods

Venous blood samples were collected within 48 h into preservative-free heparinized tubes for T cell studies (heparinized using 25 units/ml Monoparin; CP Pharmaceuticals, Wrexham, UK) and into endotoxin-free glass tubes for serum studies. Samples for endotoxin assays were allowed to clot and then centrifuged; the serum was harvested and frozen at −20°C until analysis.

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T lymphocyte studies. Density-gradient separation was performed by centrifugation for 30 min at 400g over Lymphoprep (Nycomed, Oslo, Norway). A volume of 100 μl cell suspension (1×10^6 cells/ml) was added to wells on a V bottom microtitre plate. The plate was centrifuged at 800g for 5 min at 4°C, the supernatant discarded, and the cells resuspended. An aliquot of 100 μl mouse antihuman antibody directed at the CD4 epitope (OKT4 antibody) was added to each well and incubated at 4°C for 45 min in the dark. (An antibody to a melanoma cell line, α-mel, was used as a negative control.) The cells were washed three times in phosphate-buffered saline (PBS) containing 2 per cent fetal calf serum (FCS), 2 per cent normal human serum and 10 mmol/l sodium azide. A volume of 50 μl goat antimouse immunoglobulin (Ig) G conjugated with fluorescein (Sigma Chemicals, Poole, UK) and diluted 1:150 with PBS–FCS–normal human serum–azide was added and reincubated for a further 45 min in the dark at 4°C. After three further washes the cells were fixed with PBS–FCS–normal human serum–azide containing 2 per cent formalin.

Flow cytometric analysis was performed using an EPICS V flow cytometer (Coulter Electronics, Luton, UK). Forward *versus* 90° light scatter was measured and results expressed as the percentage of CD4-positive cells in a sample of 10 000 peripheral blood mononuclear cells counted.

Endotoxin assay. Levels of endotoxin were determined using a kinetic chromogenic *Limulus* amoebocyte lysate method based on the endotoxin-specific Endospecy assay[19] (Seikagaku, Tokyo, Japan). Briefly, freshly thawed test sera were diluted 1:10 in pyrogen-free water and heated to 85°C for 15 min. Endotoxin standard (*Escherichia coli* O111 lipopolysaccharide S (1 ng, 12 endotoxin units); Kabi Diagnostica, Milton Keynes, UK) was diluted in endotoxin-free normal human serum (the negative control). Endospecy reagent was simultaneously added to test samples, standards and controls using a transfer plate. The plate was read at 405 nm (reference wavelength 650 nm) on a Maxline plate reader (Alpha Laboratories, Eastleigh, UK) at 37°C. Values >5 pg/ml are not found in sera from healthy individuals using this method (G.R.B., unpublished data).

Ig G and Ig M antiendotoxin core antibody levels were measured as described previously[17,18]. The normal ranges for Ig G and Ig M antiendotoxin core antibody were determined using blood from 1000 healthy donors and data expressed as a percentage of the control median (defined as 100 per cent).

Interleukin 6 assay. Serum IL-6 levels were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Quantikine; British Biotechnology, Slough, UK) and read at 450 nm on an ELISA plate reader (Titertek Multiscan MCC; Flow Labs, Rickmansworth, UK). This assay has a working range of 10–2000 pg/ml and an interassay coefficient of variation <10 per cent.

C-reactive protein assay. CRP was measured using an ELISA. Briefly, serum samples were diluted and incubated on microwell plates coated with an antibody fragment for antigen binding ($F(ab)_2$) prepared from a commercially available rabbit anti-CRP antibody (Dako, High Wycombe, UK). After 2 h the plate was washed and horseradish peroxidase-conjugated rabbit anti-CRP antibody (Dako) added for 1 h. After washing, the chromogen *o*-phenylenediamine in citric acid–phosphate buffer containing hydrogen peroxide was added to each well, incubated for 15 min and the reaction stopped by addition of 1 mol/l sulphuric acid. Dako CRP calibrant and serum samples were read on a Titertek Multiscan MCC plate reader at 450 nm. The sensitivity of this assay was 0·1 μg/ml with an interassay coefficient of variation of 2–15 per cent using plasma samples with CRP concentrations ranging from <1 to 400 mg/l.

All samples were run in triplicate. Data are expressed as median (interquartile range) and statistical analysis performed using the Mann–Whitney U test and paired t test as appropriate. Correlation coefficients were calculated by linear regression.

Results

Twenty-nine patients were studied: 16 suffered mild and 13 severe attacks of acute pancreatitis. The two groups were similar with respect to age and aetiology (*Table 1*). Computed tomography showed that the nine patients who survived after severe attacks had pancreatic necrosis. T cell studies were performed on all patients with severe disease and on ten with mild attacks. Serum studies were performed on all patients with mild disease and on 12 with severe attacks.

CD4 expression

Between 30 and 40 per cent of mononuclear cells expressed CD4 surface antigen in the control population. The median expression of CD4-positive mononuclear cells was 34·9 and 12·2 per cent for patients suffering mild and severe attacks respectively (*Figure 1*). A significant increase in the proportion of mononuclear cells expressing CD4 antigen was observed during convalescence in patients who had survived severe attacks (22·4 *versus* 10·6 per cent in the acute period, $P < 0.01$) (*Figure 2*).

Endotoxaemia and circulating antiendotoxin core antibodies

Circulating endotoxin was detected in only four patients (two with mild, two with severe pancreatitis) but abnormalities in levels of endogenous antibodies to the endotoxin core were common. There was a tendency for patients with severe attacks to have increased levels of Ig G antibody compared with those with mild disease (median 190 *versus* 108 per cent). This difference was not, however, statistically significant. In contrast, a significantly reduced level of Ig M antiendotoxin core antibody was found in patients suffering either severe or mild compared with healthy controls (*Figure 3*).

Interleukin 6

Serum levels of IL-6 were raised in seven of 12 patients with severe attacks but in none of those with mild disease. The serum level of IL-6 in patients with mild attacks was <10 pg/ml in

Table 1 *Patients suffering severe and mild attacks of acute pancreatitis*

	Severe (n = 13)	Mild (n = 16)
Mean(s.d.) age (years)	58·1(19·5)	59·8(16·9)
Sex ratio (M:F)	3:10	8:8
Aetiology		
Gallstones	7	14
Alcoholic	1	1
Idiopathic	3	1
Traumatic	1	0
After ERCP	1	0
Outcome		
Necrosis	12	—
Early shock	1	—
Death	4*	—

ERCP, endoscopic retrograde cholangiopancreatography. *One early death from shock and three late deaths from sepsis and pancreatic necrosis

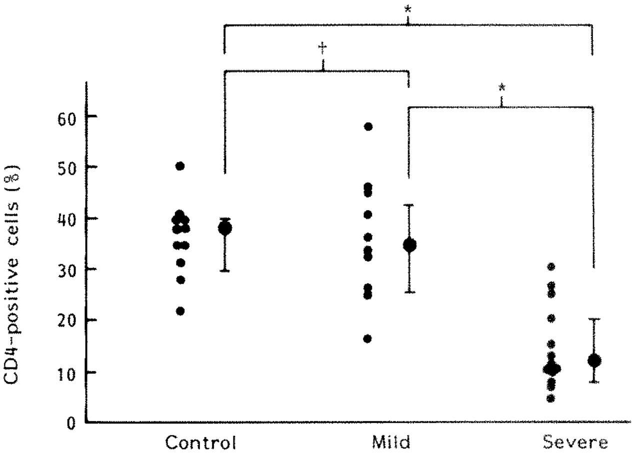

Figure 1 *Proportion of T helper cells (CD4-positive) in a sample of 10 000 peripheral blood mononuclear cells in healthy controls* (n = *11*) *and patients with mild* (n = *10*) *or severe* (n = *13*) *acute pancreatitis. Bars are median (interquartile range).* *P < *0·01;* †P *not significant (Mann–Whitney* U *test)*

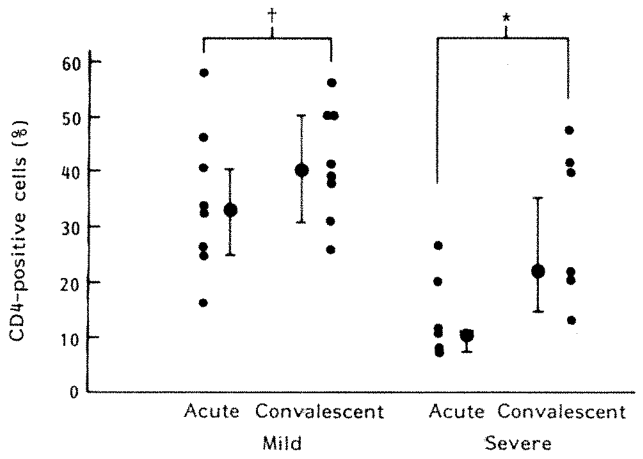

Figure 2 *Proportion of T helper cells during acute attacks and during convalescence 3 months later in patients with severe* (n = *6*) *or mild* (n = *8*) *acute pancreatitis. Bars are median* (*interquartile range*). *P < *0·01;* †P *not significant* (*paired* t *test*)

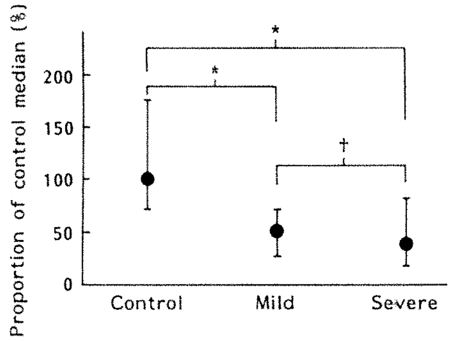

Figure 3 *Median* (*interquartile range*) *immunoglobulin M anticore glycolipid antibody levels in controls* (n = *1000*) *and mild* (n = *16*) *or severe* (n = *12*) *acute pancreatitis.* *P < *0·05;* †P *not significant* (*Mann–Whitney* U *test*)

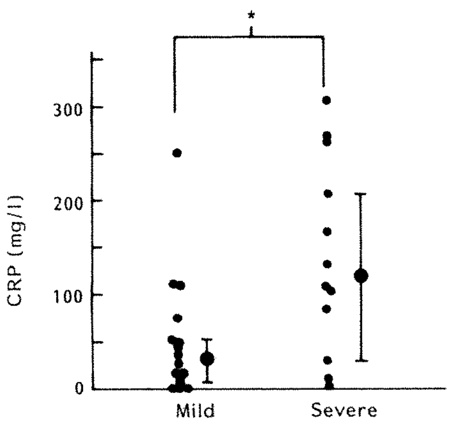

Figure 4 *Serum C-reactive protein* (*CRP*) *levels in severe* (n = *12*) *or mild* (n = *16*) *acute pancreatitis. Bars are median* (*interquartile range*). *All control samples had values < 10 mg/l.* *P < *0·01* (*Mann–Whitney* U *test*)

all but one (11 pg/ml), compared with a median of 69·5 pg/ml for patients suffering severe attacks ($P < 0·01$). IL-6 was not detected in control sera.

C-reactive protein

Raised serum levels of CRP (>10 mg/l) were found in 23 patients (*Figure 4*). There was a strong negative correlation between the percentage of CD4-positive cells and the level of CRP in patients with severe attacks ($r = -0·76$, $P = 0·004$).

Discussion

CD4-positive T helper lymphocytes are the primary source of IL-2, which is responsible in part for a variety of cellular immune responses[20–25]. The percentage of CD4-positive cells is decreased in patients with acquired immune deficiency syndrome, following thermal injury and blunt trauma[3], and after infusion of endotoxin[9]. Depressed delayed-type skin hypersensitivity reflects altered cellular immune function and correlates with septic morbidity and mortality in those with burns, trauma and acute pancreatitis[7]. Conversion from anergy to reactivity is a good prognostic sign after surgery or major trauma. Administration of recombinant IL-2 in models of burn injury returns some lymphocyte abnormalities[3,26] to normal and improves survival. The reduction in number of CD4-positive cells, and consequently lower IL-2 levels, may be partly responsible for the depressed cellular immunity seen in patients with severe acute pancreatitis.

In the present study, the decreased levels of T helper cells observed in patients with severe attacks returned towards normal in the convalescent phase, suggesting a reversible mechanism. The level of CD4-positive cells may have prognostic value in a given attack but, more importantly, suggests that immunomodulation has therapeutic potential in severe acute pancreatitis. The strong correlation between high levels of CRP and low percentage of CD4-positive cells suggests that the CD4 level is also a marker for necrosis[27].

Changes in the T cell profile may be caused by exposure to endotoxin but circulating endotoxin was demonstrated in only four patients. This may reflect the short half-life of the endotoxin molecule and the transient nature of endotoxaemia as measured by the *Limulus* assay. In contrast, changes in antibody levels persist for many days and are a better indicator of exposure to endotoxin. Endogenous antibody levels to the core determinant of endotoxin were therefore determined. An early reduction in circulating IgG antibodies to the endotoxin core may be followed by a rebound increase in IgG antibody levels[28]. Similar changes in IgM antibody levels to the endotoxin core occur, but in this case the rebound occurs earlier and is transient (G.R.B., unpublished data). In the present study, abnormal levels of IgG or IgM antiendotoxin core antibodies were found in 70 per cent of mild attacks and 92 per cent of severe attacks but an increase in serum IL-6 level was seen in severe attacks only. This may reflect a differential response to endotoxin in severe disease or may result from the occurrence of repeated episodes of endotoxaemia that were not identified.

If endotoxin is an important factor in acute pancreatitis then it probably exerts its actions via the cytokines released by monocytes. Classically, tumour necrosis factor (TNF) release has been associated with the detrimental effects of endotoxin exposure. Raised TNF levels in severe acute pancreatitis have been demonstrated[29,30]. TNF is a positive regulator[31] of IL-6, which may explain these findings. In turn, IL-6 synergizes with IL-1, promotes B cell differentiation and antibody production, promotes the acute-phase response and circulates complexed to α_2-macroglobulin[32].

This study describes immunological abnormalities in patients with acute pancreatitis and, perhaps more importantly, demonstrates immunological changes similar to those found after thermal, surgical or traumatic injury. The similarity between these conditions offers fresh hope for the management of patients with necrotizing pancreatitis. Administration of IL-2[26], cyclo-oxygenase inhibitors[33,34], and monoclonal antibodies directed against endotoxin[35] or its related cytokines[12] may prove useful in the treatment of patients with severe acute pancreatitis associated with compromised cellular immune function, high rates of septic complication and death.

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Pancreatic fistula cured by an endoprosthesis in the pancreatic duct

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Pancreatic fistula can develop in patients with chronic pancreatitis or trauma[1–3]. Symptoms from the pancreas are often absent or mild, and diagnosis usually relies on the demonstration of complications from other organs, particularly the lungs. Major pleural effusion, usually on the left side, with a high concentration of pancreatic amylase and pulmonary symptoms may be the first sign of pancreatopleural fistula. Fluid collection in the abdomen may also indicate a fistula. Endoscopic retrograde cholangiopancreatography (ERCP) is essential for the diagnosis.

Two patients with pancreatic fistula are presented, both of whom were cured by insertion of an endoprosthesis into the main pancreatic duct. Both patients had a long history of alcohol abuse.

Case reports

Patient 1

A 65-year-old man was admitted in a poor general condition. Chest radiography showed a large left pleural effusion that had not been present 1 year earlier. The fluid contained amylase at high concentration (> 20 000 units/l). The insertion of an external 10-Fr pigtail catheter into the pleural cavity was followed by the daily drainage of 800 ml fluid. ERCP (*Figure 1a*) showed a slightly abnormal main pancreatic duct, compatible with chronic pancreatitis, with a fistula arising just to the left of the spine and communicating with the left pleural cavity. A guidewire (Tracer wire guide; William Cook Europe, Bjaeverskov, Denmark) was passed through the main pancreatic duct until the tip lay 1 cm to the left of the origin of the fistula; a 5-Fr straight endoprosthesis with multiple side holes was inserted along the guidewire. Oral food intake was not restricted and the patient received no additional medication or parenteral nutrition. Secretion of fluid through the pleural stent stopped immediately after ERCP; the patient's condition improved rapidly, allowing him to leave hospital 16 days later. ERCP performed at 3 months showed no leak in the pancreatic duct (*Figure 1b*) and chest radiography was normal. Endoscopic pancreatic sphincterotomy was performed to ensure unobstructed flow and the endoprosthesis was removed. The patient remains well 10 months later.

Patient 2

A 66-year-old woman underwent abdominal ultrasonography because of a 1-year history of weight loss and abdominal discomfort. ERCP (*Figure 2a*) showed a large fistula from the main pancreatic duct extending subhepatically as far as the diaphragm. A 5-Fr endoprosthesis was placed in the pancreatic duct with the proximal end at the fistula opening, and sphincterotomy was performed using a needle papillotome along the endoprosthesis. After 2 uneventful months, during which time all abdominal symptoms subsided and the patient gained 2 kg in weight, repeat ERCP was performed. The fistula was still present but had narrowed considerably (*Figure 2b*). The common bile duct (CBD) was compressed in its intrapancreatic course, compatible with chronic pancreatitis. A second endoprosthesis was inserted to accelerate healing of the fistula. Some 2 months later ERCP (*Figure 2c*) showed complete healing with filling of the pancreatic duct beyond the level of the fistula for the first time. Compression of the CBD was unaltered but was causing no symptoms. Both endoprostheses were removed without recurrence of symptoms.

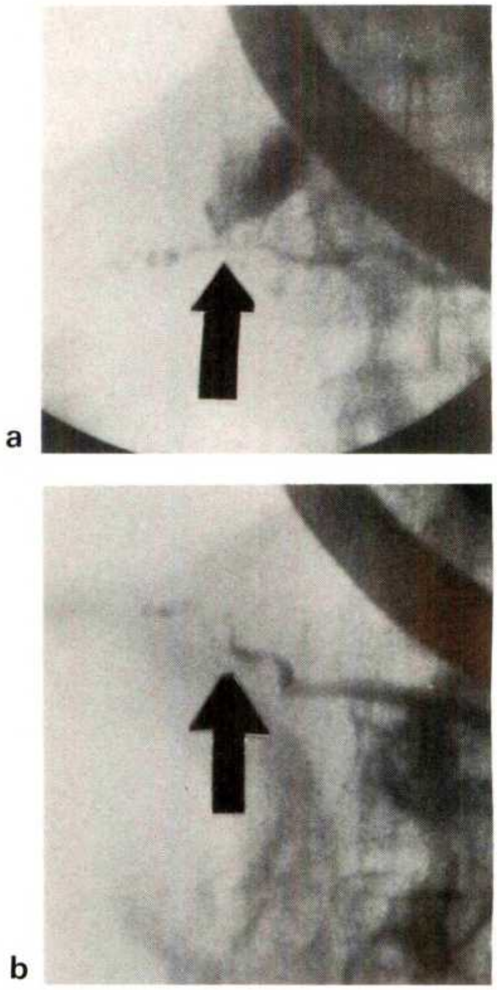

Figure 1 *Endoscopic retrograde cholangiopancreatograms (prone views) in patient 1.* **a** *A fistula from the pancreatic duct in a patient with chronic pancreatitis.* **b** *At 3 months after insertion of an endoprosthesis the fistula has closed. Arrows indicate the fistula origin*

Discussion

Two kinds of treatment have been recommended for pancreatic fistula. Somatostatin therapy plus parenteral nutrition can reduce fistula output in patients with a pancreatopleural lesion and lead to subsequent closure of the fistula in a number of patients[4,5], but it is time-consuming and expensive. Resection of the part of the pancreas to the left of the fistula is an effective but major undertaking[1,2].

In the present patients it seemed likely that secretion through the fistula would stop if the natural flow through the duct system were facilitated by relief of any blockage. Insertion of an endoprosthesis eliminated any potential obstruction by minor duct strictures or the papillary sphincter and led to prompt cessation of secretion from the fistula track with healing of the lesion within a few months. Insertion of the endoprosthesis was relatively easy once the guidewire had been passed. Tortuous and stenotic ducts can be difficult or impossible to negotiate[1], but the new Tracer wire guide greatly facilitates this manoeuvre.

This endoscopic management of pancreatic fistula is inexpensive and convenient, being similar to the method

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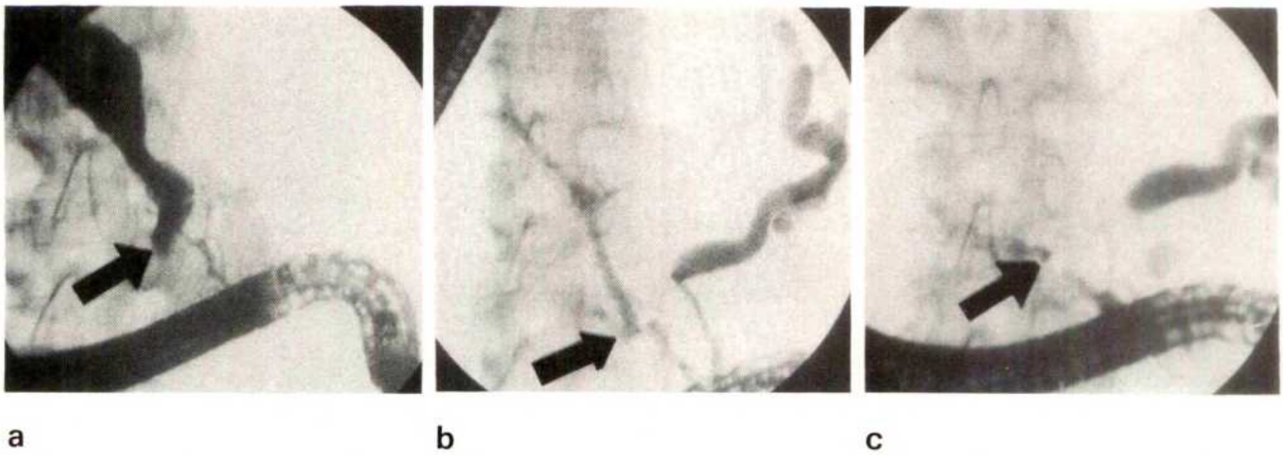

Figure 2 *Endoscopic retrograde cholangiopancreatograms (prone views) in patient 2.* **a** *A large subhepatic fistula from the main pancreatic duct.* **b** *After insertion of an endoprosthesis with its tip at the fistula opening, the lesion narrowed considerably during the following 2 months.* **c** *After 4 months the fistula was obliterated and the pancreatic duct was then filled instead. Arrows indicate the fistula origin*

advocated for treatment of biliary tract fistula[6]. As neither of the patients described had duct obstruction, except perhaps at the papilla, the rationale for performing sphincterotomy at the time of stent removal was to prevent subsequent recurrence of the fistula. The manoeuvre has proved successful in the short term.

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Effect of nifedipine on renal transplant rejection

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The effect of early nifedipine therapy on acute renal allograft rejection was studied in 170 adult cadaveric transplant recipients. Acute rejection occurring in the first 3 months after transplantation was diagnosed by Tru-cut biopsy and the severity of each rejection episode assessed histologically. The incidence of acute rejection was significantly lower in patients treated with nifedipine (29 of 80; 36 per cent) than in controls (52 of 90; 58 per cent) (P < 0·01) and there was a higher proportion of histologically mild rejection episodes in the former group (P < 0·01). Multivariate analysis confirmed that nifedipine exerted a significant independent effect on the incidence of early acute rejection. Other factors identified in the multivariate model as influencing rejection were human leucocyte antigen (HLA) matching at the DR locus, blood level of cyclosporin during the first week, HLA matching at the B locus, donor age and donor sex. The 1-year graft survival rate was 88·6 per cent in patients given nifedipine and 63·8 per cent in controls (P < 0·02). These data suggest that nifedipine therapy has a useful role in human renal transplantation.

The calcium channel blocker nifedipine relaxes vascular smooth muscle and is therefore used extensively as an antihypertensive agent. Cyclosporin therapy is often complicated by sodium-dependent hypertension and nifedipine has commonly been used in renal transplant recipients to treat this condition. Nifedipine also ameliorates cyclosporin nephrotoxicity[1] and reduces the incidence of delayed graft function after renal transplantation[2].

Recent experimental evidence suggests that nifedipine depresses a variety of functions in both the afferent and efferent limbs of the immune response[3]. The aim of the present study was to determine whether early nifedipine therapy has an effect on acute graft rejection after adult cadaveric renal transplantation. The study was limited to the first 12 weeks after transplantation as this is known to be the period in which rejection is most common.

Patients and methods

The outcome of a consecutive series of 187 cadaveric renal transplants performed between January 1986 and January 1991 was analysed retrospectively. Eleven patients who suffered non-immunological graft failure in the first week after transplantation and six who received calcium channel-blocker therapy with drugs other than nifedipine were excluded from further analysis. The 11 non-immunological failures were all caused by early thrombosis; histological analysis excluded rejection. Only four of these 11 patients were being treated with nifedipine. The remaining 170 cadaveric renal transplant recipients formed the study group.

Data recorded prospectively were retrieved from computerized unit records and UK Transplant Service files. Hospital notes and drug charts were examined retrospectively to identify the use of calcium channel blockers in the preoperative period and in the 12 weeks after transplantation. Nifedipine was prescribed for hypertension according to clinical need. The dose used (10–40 mg twice daily) was determined by the severity of hypertension. The influence of the following variables on rejection rates was studied: recipient age and sex; cause of renal failure; hypertensive status; current type of dialysis; number of previous transplants; donor age, sex and blood group; first warm ischaemia time; second warm ischaemia time (anastomosis time); cold ischaemia time; presence of panel-reactive lymphocytotoxic antibodies in current and historical recipient sera; human leucocyte antigen (HLA) mismatch between recipient and donor at the A, B and DR loci (scored 0–6); and type of immunosuppression used.

Immunosuppression protocol

In the first year of the study, patients received conventional immunosuppressive therapy using azathioprine (2–3 mg per kg per day) and low-dose steroids (starting at 20 mg/day gradually decreasing to 10 mg/day by 6 months after transplantation). Cyclosporin therapy was used in all other patients at a dose of 10–15 mg per kg per day either in combination with low-dose steroids or as part of triple therapy with steroids and azathioprine.

Whole-blood cyclosporin levels were measured using a radioimmunoassay kit with doses being adjusted to maintain trough levels in the range 400–800 ng/ml.

Acute rejection episodes occurring during the 12 weeks after transplantation (early acute rejection) were recorded. Acute graft rejection was defined using a combination of clinical findings (graft tenderness or swelling; pyrexia; diminishing urine output; response to steroid pulsing), biochemical data (serum creatinine and whole-blood cyclosporin levels) and the results of allograft histology (Tru-cut needle biopsy; Travenol Laboratories, Thetford, UK). Only one patient with suspected rejection was not submitted to Tru-cut biopsy, for technical reasons. The histological severity of rejection was classified as mild, moderate or severe according to the density of the mononuclear cell infiltrate. First rejection episodes were treated by three daily pulses of 0·5 g intravenous methylprednisolone. Steroid-resistant or particularly severe rejection episodes were treated with a 10–14-day course of either the monoclonal antibody OKT3 (Cilag, High Wycombe, UK) or horse antilymphocyte globulin (Merieux, Maidenhead, UK). Patients were followed routinely in the transplant clinic and form a consecutive series apart from the exclusions stated.

Statistical analysis

Univariate statistical analysis was performed using the χ^2 test for categorical variables and Student's unpaired t test for continuous variables. Multivariate analysis involved use of the Epidemiological Graphics Estimation and Testing (EGRET) package (Research Corporation, Seattle, Washington, USA). Stepwise Cox regression analysis was performed to determine factors independently associated with the development of acute rejection. All factors except calcium channel-blocker therapy were initially eligible for inclusion; this allowed assessment of the effect of calcium channel blockers *per se*. Patients lost to follow-up within the first 12 weeks were censored at the point at which they were last seen.

The effects of individual variables on graft survival were analysed by plotting Kaplan–Meier[4] curves and the statistical significance of differences determined using the log rank test[5]. Graft loss was defined

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as patient death, retransplantation or return to dialysis. Death from any cause was included in the analysis.

Results

Data from 170 renal transplants were available for analysis. These were performed in 114 men and 56 women of mean(s.d.) age 40·5(13·3) (range 16–70) years. Fifty-four patients were ≥50 years of age. Immunosuppressive treatment given was azathioprine and prednisolone in 32 patients, cyclosporin and prednisolone in 117 and triple therapy in 21.

Eighty patients received oral nifedipine therapy (10–40 mg twice daily) in the first 12 weeks after transplantation; 46 were already taking nifedipine at the time of admission for transplantation and 34 were started on therapy in the first 2 weeks after operation. Ninety patients did not receive nifedipine at any time during the 12 weeks after transplantation. The immunological and demographic characteristics of these two study groups are shown in *Table 1*. There were no statistically significant differences in the level of HLA mismatching or type of immunosuppression used. There was no difference in the mean(s.e.m.) dose of cyclosporin used during the first 12 weeks in patients receiving nifedipine compared with controls (6·02(0·27) *versus* 5·35(0·34) mg per kg per day, $P = 0{\cdot}13$) nor any difference between the mean(s.e.m.) whole-blood levels of cyclosporin (340(30) *versus* 320(28) ng/ml, $P = 0{\cdot}63$).

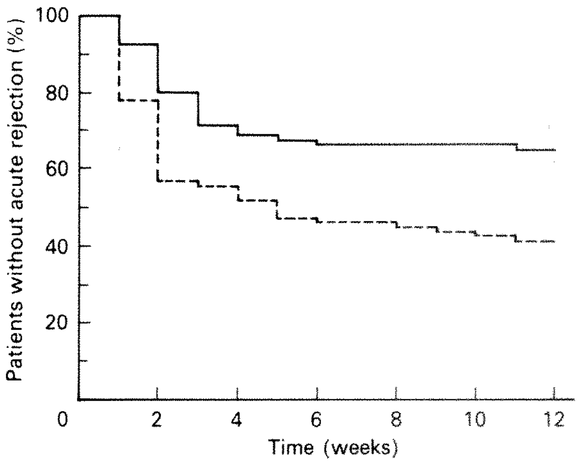
Incidence and severity of rejection

In the 80 patients receiving nifedipine there were 32 acute rejection episodes in 29 patients (26 had one rejection, three had two). In the control group of 90 patients there were 73 rejection episodes in 52 patients (35 had one rejection, 13 had two episodes, four had three). The proportion of patients with at least one episode of acute rejection was significantly lower for those given nifedipine (29 of 80 (36 per cent) *versus* 52 of 90 (58 per cent); $\chi^2 = 7{\cdot}87$, 1 d.f., $P < 0{\cdot}01$). A Kaplan–Meier plot showing the time to first acute rejection confirmed a significant reduction in rejection rate in patients treated with nifedipine (log rank $\chi^2 = 9{\cdot}52$, 1 d.f., $P = 0{\cdot}002$; *Figure 1*).

Analysis of the histological severity of rejection demonstrated less severe episodes in patients treated with nifedipine (*Table 2*). This was the result of a higher proportion of mild and a lower proportion of moderate rejections; there was no difference in the number of severe episodes. Six patients in each group required treatment with OKT3.

Multivariate analysis

The final model obtained in the Cox regression analysis included: HLA mismatches at the DR locus, blood level of cyclosporin in the first week, HLA-B mismatches, donor age, donor sex and nifedipine therapy (*Table 3*). Matching at the HLA-DR locus had the most powerful effect. None of the other variables examined significantly improved the fit of the model. The first-week and 3-month readings for cyclosporin dose and blood level were modelled as continuous variables. Patients receiving cyclosporin after the first week were coded as zero for the first-week reading of both cyclosporin dosage and blood level. Initially, ten patients were excluded from the analyses



No. at risk			
Nifedipine	55	53	50
Controls	46	39	36

Figure 1 *Kaplan–Meier curve of time to first acute rejection showing the effect of nifedipine therapy. The curve is based on data from 170 patients; those with transplant failure were censored.* ——, *Patients treated with nifedipine;* – – –, *controls.* P = *0·002 (log rank test)*

Table 2 *Severity of rejection episodes*

	Nifedipine	Controls
Mild	11 (34)	6 (9)
Moderate	14 (44)	44 (64)
Severe	7 (22)	19 (28)
Total	32	69*

Values in parentheses are percentages. * Four episodes of rejection were not graded histologically. $\chi^2 = 10{\cdot}4$, 2 d.f., $P < 0{\cdot}01$

Table 1 *Patient details*

	Nifedipine ($n = 80$)	Controls ($n = 90$)	Statistics		
			χ^2	t	P
Recipient sex*					
M	58 (72)	56 (62)	2·03		0·15
F	22 (28)	34 (38)			
Recipient age (years)†	37·8(13·3)	43·0(13·0)		−2·56	<0·01
Donor age (years)†	32·0(13·9)	37·4(15·7)		−2·31	<0·02
Cold ischaemia time (h)†	19·8(7·9)	18·2(7·7)		1·34	0·18
Anastomosis time (min)†	35·1(9·7)	38·6(11·9)		−2·08	0·04
First transplant*	65 of 80 (81)	72 of 90 (80)	0·04		0·84
Sensitized patients*‡	14 of 78 (18)	17 of 90 (19)	0·02		0·88
Hypertension*	61 of 80 (76)	45 of 90 (50)	12·4		<0·001
Transplant*					
Initial function	70 (88)	58 (64)	12·1		<0·001
Primary non-function	10 (12)	32 (36)			

*Values in parentheses are percentages; †values are mean(s.d.); ‡ ≥50 per cent panel-reactive antibodies (highest serum)

Table 3 *Multivariate analysis*

Variable	No. with rejection	No. without rejection	Hazard ratio: Unadjusted	Hazard ratio: Adjusted
HLA-DR mismatches				
0	62	22	1·00	1·00
1	20	34	3·56 (2·08–6·11)	4·85 (2·66–8·84)
2	2	13	7·77 (3·85–15·67)	8·64 (3·80–19·64)
HLA-B mismatches				
0	26	3	1·00	1·00
1	33	30	5·63 (1·72–18·46)	5·70 (1·68–19·41)
2	25	36	8·77 (2·70–28·53)	5·51 (1·64–18·52)
Nifedipine therapy				
Yes	48	27	1·00	1·00
No	36	42	1·80 (1·11–2·92)	1·62 (0·98–2·68)
Donor sex				
M	60	44	1·00	1·00
F	24	25	1·31 (0·80–2·14)	1·72 (1·02–2·90)
Donor age (per year)	—	—	1·01 (1·00–1·03)	1·02 (1·00–1·04)
Cyclosporin level (per ng/ml) (first week)	—	—	0·999 (0·998–1·000)	0·998 (0·997–0·999)

Values in parentheses are 95 per cent confidence intervals. The final model was based on 153 observations. HLA, human leucocyte antigen

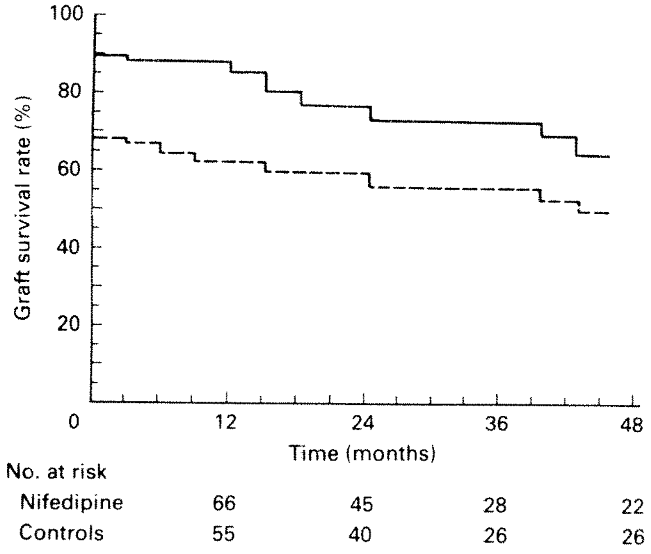


Figure 2 *Kaplan–Meier curve showing the effect of nifedipine therapy on renal transplant survival.* ——, *Patients treated with nifedipine;* – – –, *controls.* P = *0·01 (log rank test)*

since there were no 3-month readings for cyclosporin dose and blood level; these patients were lost to follow-up before this time point. Since it was found that neither cyclosporin dose nor blood level at 3 months was associated with rejection the model was refitted on the larger database including these ten patients. The final model obtained is therefore based on 153 observations. The addition of polynomial terms for donor age and cyclosporin level in the first week did not improve the fit of the model significantly.

The hazard ratios in *Table 3* are a measure of the association between each variable and rejection. The adjusted hazard ratios include the effects of all items in the model, as described above. For categorical variables a hazard ratio is given for each level of the variable apart from the first, which defines the baseline value. Each hazard ratio thus indicates how much more or less likely it is for a patient to suffer graft rejection. For example, patients not receiving nifedipine therapy are 1·62 times more likely to experience acute rejection than those given the drug. The hazard ratios for the continuous variables in *Table 3* indicate how much the risk of rejection changes for every incremental increase of the continuous variable. For example, the risk of rejection increases 1·02 times for every 1-year rise in the age of the donor. A 10-year-old donor is therefore associated with a $1·02^{10}$ (i.e. 1·22) times higher risk than a 1-year-old donor.

Renal function

Serum creatinine levels were lower in patients treated with nifedipine at 3, 6, 12 and 24 months after transplantation, but the differences were not statistically significant at the 5 per cent level.

Graft survival

Fourteen of the 80 transplants (18 per cent) in patients given nifedipine failed; there were nine graft losses resulting from rejection, four non-immunological graft losses and one death. Twenty-nine of the 90 control transplants (32 per cent) failed; there were 22 secondary to rejection, six non-immunological losses and one death. Graft survival was significantly better in patients treated with nifedipine than in controls (log rank $\chi^2 = 7·91$, 1 d.f., $P = 0·01$; *Figure 2*). The 11 early graft losses that resulted from non-immunological failure were included in the data used to produce *Figure 2*.

Discussion

The molecular events that lead to T cell activation and proliferation suggest a basis for the immunosuppressive action of nifedipine. Acute cellular rejection is mediated by T lymphocytes, the process being initiated by the presentation of foreign antigen to helper T cells in the allograft. This process leads to T lymphocyte activation, the production of cytokines such as interleukin (IL) 2, the expression of IL-2 receptors on the cell surface and proliferation into a clone of cytolytic T cells. *In vitro* studies have shown that the influx of calcium ions across the lymphocyte membrane is a critical factor in the activation of T cells by mitogens[6,7]. In addition, mitogen-stimulated lymphocyte proliferation is inhibited by a calcium-free medium and inactive lymphocytes become reactivated only when calcium is reintroduced[8].

It can therefore be hypothesized that nifedipine reduces the immune response to an allograft by limiting the transmembrane flux of calcium that is important for lymphocyte activation and proliferation. Evidence to support this theory comes from *in vitro* studies, which have demonstrated that the calcium channel blockers verapamil, nifedipine and diltiazem exhibit a dose-dependent suppression of mitogen-stimulated T cell proliferation[9–12]. Indeed, this finding has been confirmed for nicardipine and diltiazem therapy in humans[13]. Verapamil also decreases the cytolytic capability of T cells and natural killer cells[12].

The mechanism of action of the immunosuppressant effect of the calcium channel blockers can only be hypothesized, although for verapamil at least there is evidence to suggest that IL-2 production and expression of IL-2 receptors are not involved[3]. The immunosuppressant action of calcium channel blockers may involve a non-calcium channel-dependent mechanism[3].

The results of the present analysis concur with those of a small randomized study of the effects of early treatment with verapamil[14], in which significantly fewer patients given verapamil were treated for rejection than in a control group (three of 22 *versus* ten of 18). The mechanism of action may differ as verapamil is known to increase blood levels of cyclosporin, whereas nifedipine has no effect on the haemodynamics of cyclosporin[15]; this finding is confirmed in the present study.

Improved renal function has been associated with nifedipine therapy previously[16,17] and may be a direct effect of reduced graft rejection, a result of reduced cyclosporin nephrotoxicity[1] or a combination of both. The diagnosis of cyclosporin toxicity is a rather complicated process of exclusion and it is impossible to quantify the role of each factor in improving renal function. Although significantly better graft survival was demonstrated in patients treated with nifedipine it is not certain that this results from the effects of the drug *per se*. For this issue to be settled, a Cox regression analysis of the survival data would have to be performed to allow for differences in other baseline variables. That nifedipine has an immunosuppressive effect adds an exciting new dimension to the use of this drug. A large randomized trial is now required.

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Cytokine gene transcription in renal cell carcinoma

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Cytokines are powerful modulators of immune responses, the local production of which could be relevant to the interaction between tumour and immune system. This study investigated the transcription of genes encoding interleukin (IL) 2, IL-4, IL-10 and interferon (IFN) γ in lymphocyte-infiltrated renal cell carcinoma biopsies from ten patients using the reverse polymerase chain reaction technique. Autologous peripheral blood mononuclear cells and healthy renal parenchyma tissue were tested in parallel. The β-actin gene, used as a positive control, was transcribed in all samples. In contrast, transcription of cytokine genes was confined to tumour biopsies: IL-2 gene transcripts were detectable in five biopsies and IL-10 transcripts in seven. IL-4 and IFN-γ gene transcripts were detectable in one biopsy each. In two patients no cytokine gene transcription could be identified. These data underline that heterogeneous patterns of cytokine gene transcription can be observed in renal cell carcinoma biopsies. Although transcription of an immunostimulatory lymphokine such as IL-2 was observed in 50 per cent of biopsies, the most frequently transcribed cytokine gene coded for an inhibitory factor, IL-10.

Most human neoplasms are infiltrated by lymphocytes[1]. Cultured tumour-infiltrating lymphocytes have been used in clinical trials evaluating adoptive immunotherapy in neoplastic disease[2], but the nature of the interaction between such lymphocytes and tumour cells is unclear.

Lymphocyte infiltration of tumours might result from recognition by T cells of specific antigens. A tumour-specific antigen has been identified in melanoma and its sequence determined[3], and the T cell receptor variable region usage in tumour-infiltrating lymphocytes has been shown to differ from that in autologous peripheral blood mononuclear cells[4,5]. These data suggest the possibility of antigen-driven T cell selective events. Evidence that tumour-infiltrating lymphocytes express typical surface activation markers, different from those of autologous peripheral blood mononuclear cells, has been reported[6,7]. Taken together, these findings characterize tumour-infiltrating lymphocytes as an activated cell population, possibly because of antigenic stimulation.

Under physiological conditions, lymphocyte triggering is accompanied by the production of cytokines, which play a crucial role in the generation of antitumour cytotoxic activity[8]. Production of inhibitory and stimulatory cytokines has been observed in neoplastic cells, and this may have an impact on immune responses. For example, depressed immune responsiveness in patients with glioblastoma has been related to the production of transforming growth factor β_2 by tumour cells[9]. Conversely, neoplastic cell line transfection with interleukin (IL) 2, IL-4 or interferon (IFN) γ genes[10–12] has been shown to induce vigorous and long-lasting antitumour immunity.

To obtain data reflecting *in vivo* cytokine gene transcription, without risk of the artefacts inherent in cell separation or culture, the transcription of genes coding for IL-2, IL-4, IL-10 and IFN-γ was investigated in freshly excised lymphocyte-infiltrated renal cell carcinoma biopsies. Reverse polymerase chain reaction (PCR) technology, characterized by extreme sensitivity in the detection of small amounts of messenger RNA, was employed.

Patients and methods

Ten consecutive patients (seven men, three women) undergoing surgical treatment for renal cell carcinoma were studied. The mean(s.d.) age was 66(11) (range 50–82) years. Primary tumours were studied in eight patients and bone metastases in two. Tumour biopsies and, when possible, normal tissue from the affected kidney and peripheral blood mononuclear cells were collected simultaneously at the time of surgery.

Flow cytometry

Single-cell suspensions were obtained by enzymatic treatment of surgical biopsies, as previously described[7]. Tissues were finely minced and incubated at room temperature for 2 h in RPMI 1640 (Gibco, Paisley, UK) containing 0·1 per cent (w/v) collagenase type IV, 2·4 units ml^{-1} hyaluronidase type V and 0·01 per cent (w/v) DNAse (all from Sigma Chemicals, St Louis, Missouri, USA). Cells were washed and stained with optimal dilutions of commercial fluorochrome-labelled monoclonal antibodies directed against cluster differentiation (CD)3, CD69, human leucocyte antigen (HLA) DR (Becton–Dickinson, Mountain View, California, USA) or CD45RO (Dako, Glostrup, Denmark) surface determinants. After 30 min incubation at 4°C, cells were extensively washed and analysed using a FACScan flow cytometer (Becton–Dickinson). Peripheral blood mononuclear cells were separated from venous blood by gradient centrifugation on Lymphoprep (Nycomed, Oslo, Norway) using standard techniques. Staining and fluorescence analysis were performed following identical procedures as per autologous tumour-infiltrating lymphocytes. Data obtained in double-fluorescence assays are reported as percentages of CD3$^+$ lymphocytes derived from either source, expressing the activation markers indicated.

Polymerase chain reaction assays

Total RNA was extracted from intact surgical biopsies, by the methods of Chomczynski and Sacchi[13], within 1 h of excision or sampling because of the extreme lability of the transcripts of the cytokine genes[14]. RNA (1 μg ml^{-1}) was reverse transcribed using Moloney murine leukaemia virus reverse transcriptase (200 units) in the presence of oligodeoxythymidine and deoxynucleotide triphosphates (all from BRL, Gaithersburg, Maryland, USA) according to the manufacturer's instructions. The resulting complementary DNAs (cDNAs) were assayed for the presence of cytokine transcripts in PCR assays performed in 20-μl volumes (Gene-Amp kit; Perkin-Elmer-Cetus, Norwalk, Connecticut, USA) in the presence of pairs of specific primers. Sequences of the primers used are shown in *Table 1*. Primers were designed to amplify sequences from different exons, to detect eventual

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Table 1 *Nucleotide sequences of primer pairs*

Gene	Sense primer	Antisense primer	No. of base pairs of amplified fragment
β-actin	TGACGGGGTCACCCACACTGTGCCCATCTA	CTAGAAGCATTGCGGTGGACGATGGAGGG	661
Interleukin 2	ATGTACAGGATGCAACTCCTGTCTT	GTCAGTGTTGAGATGATGCTTTGAC	458
Interleukin 4	ATGGGTCTCACCTCCCAACTGCT	CGAACACTTTGAATATTTCTCTCTCAT	456
Interleukin 10	AAGGCATGCACAGCTCAGCACT	TCCTAGAGTCTATAGAGTCGCCA	575
Interferon γ	ATGAAATATACAAGTTATATCTTGGCTTT	GATGCTCTTCGACCTCGAAACAGCAT	494

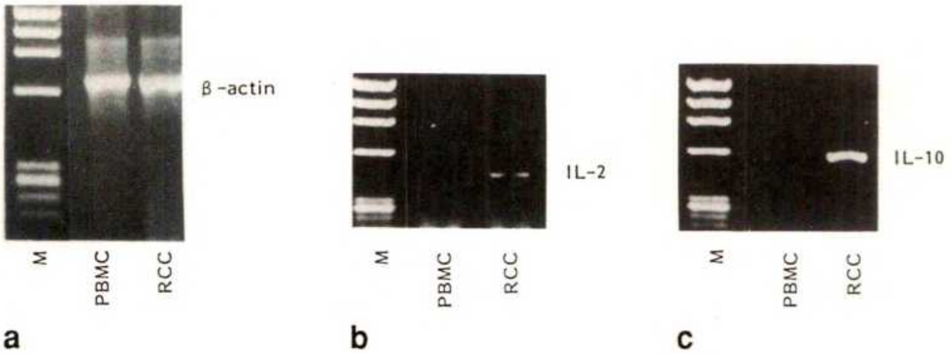

Figure 1 *Cytokine gene transcription in peripheral blood mononuclear cells (PBMCs) and tumour biopsy in patient 6. Total RNA was extracted from the PBMCs and tumour biopsy simultaneously obtained at the time of surgery from renal cell carcinoma (RCC).* **a** *β-actin amplified cDNA;* **b** *and* **c** *products of polymerase chain reactions performed in the presence of primers specific for interleukin (IL) 2 and IL-10 respectively. M, molecular weight markers*

Table 2 *Transcription of cytokine genes*

Patient no.	Tissue	β-actin	Interferon γ	Interleukin 2	Interleukin 4	Interleukin 10
1	Renal cell carcinoma	+	−	+	−	−
2	Renal cell carcinoma	+	−	−	−	+
3	Renal cell carcinoma	+	−	+	−	+
4	Healthy renal parenchyma	+	−	−	−	−
	Renal cell carcinoma	+	+	+	−	+
5	Peripheral blood mononuclear cells	+	−	−	−	−
	Renal cell carcinoma	+	−	−	+	+
6	Peripheral blood mononuclear cells	+	−	−	−	−
	Renal cell carcinoma	+	−	+	−	+
7	Peripheral blood mononuclear cells	+	−	−	−	−
	Healthy renal parenchyma	+	−	−	−	−
	Renal cell carcinoma	+	−	−	−	+
8	Peripheral blood mononuclear cells	+	−	−	−	−
	Healthy renal parenchyma	+	−	−	−	−
	Renal cell carcinoma	+	−	−	−	−
9	Peripheral blood mononuclear cells	+	−	−	−	−
	Healthy renal parenchyma	+	−	−	−	−
	Renal cell carcinoma	+	−	−	−	−
10	Peripheral blood mononuclear cells	+	−	−	−	−
	Healthy renal parenchyma	+	−	−	−	−
	Renal cell carcinoma	+	−	+	−	+

+, Detectable transcription; −, no detectable transcription

amplification of contaminating genomic DNA. PCR consisted of 35 cycles, each including 40 s denaturation at 94°C, 40 s annealing at 62°C and 1 min extension at 72°C. PCR products were subsequently run on 1·5 per cent agarose gels in Tris-buffered ethylenediamine tetra-acetic acid in the presence of ethidium bromide, and photographs taken on ultraviolet transillumination. Specificity of amplified transcripts was validated by correspondence to the expected size of cDNA sequences and by restriction mapping[15] (data not shown).

Results

Phenotypic analysis of tumour-infiltrating lymphocytes

Freshly derived tumour-infiltrating lymphocytes were evaluated and compared with autologous peripheral blood mononuclear cells for surface expression of activation markers in five patients under investigation. The proportion of $CD3^+$ tumour-infiltrating lymphocytes expressing CD69 or HLA-DR was significantly higher than that detectable in simultaneously sampled peripheral blood $CD3^+$ lymphocytes (mean(s.d.) $CD69^+$ 18(11) per cent in peripheral blood *versus* 68(25) per cent in tumour-infiltrating lymphocytes; $HLA\text{-}DR^+$ 8(5) *versus* 54(5) per cent). In addition, a surface marker characteristic of memory T cells (CD45RO) was found to be expressed in higher mean(s.d.) proportions of $CD3^+$ tumour-infiltrating lymphocytes than in autologous peripheral $CD3^+$ cells (75(21) *versus* 45(15) per cent).

Cytokine gene transcription

Total RNA extracted from freshly excised tumour biopsies was reverse transcribed and assayed in 35 cycles of PCR for the presence of transcripts of defined cytokine genes. *Figure 1* shows the results of a representative assay (patient 6). Transcripts for the β-actin gene could be amplified from cDNA derived from both peripheral blood mononuclear cells and tumour biopsy (*Figure 1a*), whereas IL-2 and IL-10 gene transcription was detected only in cDNA derived from the tumour biopsy (*Figure 1b* and *c*). *Table 2* shows the results. Transcription of the β-actin gene, tested as a positive control, was observed in all samples under investigation. In contrast, cytokine gene transcripts were never detectable in RNA from peripheral blood mononuclear cells ($n = 6$) or healthy renal tissue ($n = 5$). Transcription of IL-4 and IFN-γ genes was observed in only one biopsy, whereas IL-2 gene transcripts were detectable in five patients. IL-10 gene transcription was observed in seven biopsies.

Discussion

Tumour-infiltrating lymphocytes often express activation markers[6,7]. Antigen-driven triggering of T cells, however, would be expected to induce surface expression of activation and transcription of cytokine genes. Production of these soluble factors by immunocompetent cells plays a key role in the generation of an effective immune response.

Cytokine gene transcription was therefore examined in freshly excised tumour biopsies with lymphocyte infiltration, thereby avoiding possible cell separation and culture artefacts. The relatively low sensitivity of conventional Northern blot and *in situ* hybridization techniques did not allow demonstration of specific gene transcripts. Reverse PCR was therefore used. Renal cell carcinoma was chosen as this neoplasm may be a promising target for immunotherapy[16].

Transcription of IL-2, IL-4 and IFN-γ genes was studied because these cytokines are essential in the proliferation and functional activation of different T cell subsets[17–19]. IL-10 was studied because of its capacity to inhibit T cell proliferation and cytokine production[19–22].

The present results indicate that, despite infiltration by lymphocytes displaying surface activation markers and the use of a technique of extreme sensitivity, transcription of the cytokine genes under investigation shows wide variation in different renal cell carcinoma biopsies. In particular, transcription of IL-4 and IFN-γ genes was rarely detectable in lymphocyte-infiltrated neoplastic tissue. These data do not correlate with the pattern of cytokine gene transcription usually detectable on antigen receptor-triggered T cell stimulation *in vitro* or *in vivo*[14,15].

Regarding biopsies where cytokine gene transcription could be detected, PCR does not allow identification of the cells transcribing a given gene, and no further speculation is warranted. Irrespective of the cell type(s), however, where cytokine gene transcription takes place, these factors are able to affect the local immune response profoundly[9–12]. In particular, IL-2 and IL-10, whose gene transcripts are detected most frequently, display virtually opposite functional effects. IL-2 induces T lymphocyte proliferation and IFN-γ production; IL-10 inhibits these activities[21,22] and, together with TGF-β, is one of the two immune response inhibitory factors cloned to date. IL-2 and IL-10 have been reported to be produced by different T cell populations, albeit not clearly defined in their phenotypic profile[20]. The IL-10 gene has recently been found to be predominantly transcribed in ovarian cancer biopsies[23].

Taken together, the data suggest that patients with renal cell carcinoma do not show a homogeneous pattern of cytokine gene transcription. Interaction between tumour-infiltrating lymphocytes and neoplastic cells could result in different functional events. Further investigation is needed to address the issue of whether differential cytokine gene transcription has an influence on the clinical course of neoplastic disease or is of prognostic significance for immunotherapy procotols.

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Case report

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Localized argyria: a complication of the repair of inguinal hernia with silver filigree

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Localized argyria, the focal deposition of silver within tissues, is found most frequently in the oral mucosa following the accidental implantation of dental amalgam ('amalgam tattoo'). It has also been reported in the skin following accidental implantation by silversmiths, and with the use of silver earrings[1,2].

This paper reports a patient with localized argyria in the soft tissues of the inguinal canal following hernia repair with a silver filigree.

Case report

A 62-year-old man presented with a recurrent inguinal hernia, which had been repaired 30 years previously in another hospital in which the fashion was to insert a silver mesh. The patient had noticed a gradual breakdown in the repair over a 2-year period. At operation, a direct recurrence was repaired with nylon darn. All the tissues were firmly stained with a dense black substance; on closer inspection, fragments of metal were found. As much of the material as possible was removed for histological examination. There were no postoperative complications.

Routine histological sections showed a striking deposition of black granular refractile pigment in the walls of blood vessels, around nerves, and along collagen fibres in stromal tissue. These features are typical of argyria and reminiscent of the pattern of silver staining characteristic of the histochemical method for reticulin. There was a mild focal inflammatory reaction and only minor focal scarring.

Ultrastructural examination showed electron-dense deposits distributed around individual cells and along collagen fibres (*Figure 1*). Electron probe microanalysis of the involved tissue revealed large X-ray emissions corresponding to silver, and smaller emissions corresponding to selenium and sulphur.

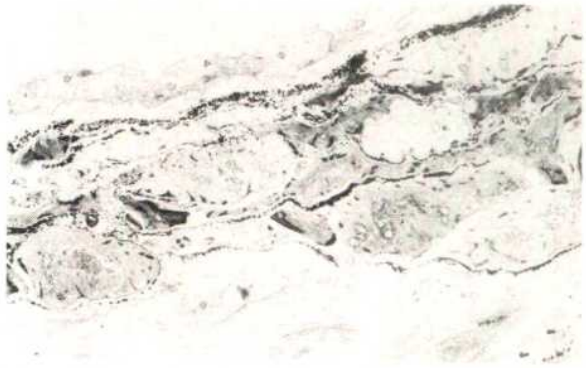

Figure 1 *Electron micrograph of a small blood vessel wall showing black granular silver deposits.* (*Original magnification* × *4400*)

Discussion

Localized argyria must be distinguished from generalized argyria, which typically follows oral ingestion of silver salts, local medicinal application to mucous membranes or occupational exposure to silver, producing systemic deposition of silver and diffuse cutaneous pigmentation. Localized argyria follows implantation of silver and most commonly occurs after the accidental introduction of dental amalgam into the mouth[1,2].

The repair of hernia with a silver filigree was described by McGavin[3] in 1909. The technique was frequently used at the Seamen's Hospital in Greenwich, the filigree mesh being made up on a jig by the theatre nurses in their spare time. It was thought that the irritant nature of the silver wire provoked an inflammatory reaction and fibrosis, and thus a stronger repair[4].

It is recognized that the silver filigree breaks down over the ensuing years with stress fractures, so that many surgeons must have been presented with cases to salvage. While reports of the results of secondary repair are available, there are no descriptions of black pigmentation in the surrounding tissues, although in the present authors' experience this is an invariable finding at re-exploration.

Documentation of this unusual and previously unrecorded phenomenon may alert surgeons to the nature of the pigmentation in the soft tissues of the inguinal canal after silver filigree hernia repair.

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Faecal occult blood screening for patients with gastrointestinal symptoms

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A practical faecal occult blood (FOB) test as a screening tool for colonic pathology was first described by Greegor[1] in 1967. Many subsequent studies have examined the accuracy and value of FOB testing as a screening method for colonic carcinoma in an asymptomatic population[2–4]. Since the role of FOB testing in patients with gastrointestinal symptoms has not yet been clearly defined, the present study was undertaken to examine this question.

Patients and methods

All patients referred by their general practitioner with a history of lower abdominal pain or a change in bowel habit were screened to assess the urgency of investigation. On receipt of the practitioner's referral letter a Haemoccult (Roehm, Darmstadt, Germany)[5,6] FOB testing kit was posted to the patient. Those with obvious rectal bleeding and those with known colonic pathology were excluded from the study. Patients were not required to follow any dietary restrictions and were asked to provide stool specimens on 3 consecutive days, applied to Haemoccult slides. The slides were returned by post and analysed as soon as possible without rehydration[3,6]. All patients subsequently gave a full clinical history, and a clinical examination (including rectal examination and rigid sigmoidoscopy) was carried out. Further investigations were performed at the discretion of the clinician, but all patients with positive FOB tests underwent flexible colonoscopy or, occasionally, barium enema examination. The study was started in July 1985 and accrual closed in July 1990.

Results

Tests were posted to 518 patients; 458 were returned correctly completed, a compliance rate of 88 per cent. In all, 51 tests (11 per cent) were positive for FOB and 407 (89 per cent) negative. Colonic pathology was found in 32 of the 51 patients with positive tests, but no pathology has so far been detected in the remaining 19. Of the 407 patients with negative FOB tests, 39 have been found to have colonic pathology and 368 remain without known pathology. The median duration of follow-up is 4 years 7 months. The test has a specificity of 95 per cent with 19 false-positives, and the sensitivity is 45 per cent with 39 false-negatives.

Colonic pathology included 23 carcinomas, 22 polyps and 27 cases of histologically proven inflammatory bowel disease (IBD). One patient had both a polyp and IBD; haemorrhoids were not regarded as significant colonic pathology. Of the 23 patients with carcinoma, 19 had positive results with Haemoccult but there were four false-negative tests (sensitivity 83 per cent). In the group of 22 patients with polyps, only two had positive tests; of the 27 patients with IBD, 11 tested positive.

Four caecal tumours were detected, three of which gave positive Haemoccult results. Two carcinomas in the ascending colon, two in the left colon and six in the sigmoid all gave positive tests. Of nine rectal carcinomas, six tested positive. The interval between the last specimen and the test being carried out was a maximum of 6 (median 3) days in the false-negative cases. Haemoccult failed to detect 17 per cent of right-sided carcinomas and 33 per cent of rectal tumours.

Discussion

The high specificity (95 per cent) of FOB testing with Haemoccult compares favourably with values in the literature of 96–98 per cent[2–4]. The low overall sensitivity of 45 per cent reflects the very low sensitivity for polyps (9 per cent). It has been shown[5] that small polyps are less prone to bleeding and therefore less likely to be detected, but the sensitivity for carcinoma alone was much greater (83 per cent) and in line with results of other studies (68–80 per cent)[2,6,7]. One-third of rectal carcinomas were missed, a number similar to the findings of Thomas *et al.*[8]. These authors also found that 44 per cent of right-sided carcinomas were not detected; one-sixth of such tumours were missed in the present study. Symptomatic patients showed a much higher incidence of carcinoma in those testing positive for FOB (37 per cent *versus* 5–10 per cent for asymptomatic patients), but the predictive value for polyps was much lower (4 *versus* 20 per cent)[5].

This study shows that a positive Haemoccult test in the symptomatic patient is a strong indicator for urgent colonic investigation since the test has a high specificity, but a negative result does not adequately exclude colonic pathology in the symptomatic patient since the test has a low sensitivity. Haemoccult testing in the symptomatic patient serves only as a guide to the urgency of investigation.

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Delay in the diagnosis and prognosis of carcinoma of the right colon

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Of 152 consecutive patients with carcinoma of the right colon, 61 (40 per cent) suffered delays in treatment of more than 12 weeks from the onset of symptoms, with a mean delay of 48 weeks. The most common error was failure to initiate or complete the investigation of iron-deficiency anaemia (33 patients). False-negative barium enema investigations occurred in 16 cases. Patients with delays in diagnosis had survival rates not significantly different from those who presented early. Thirty-one patients with anaemia and no abdominal symptoms had a significantly higher survival rate than 30 presenting with abdominal symptoms, despite delays in treatment ($P < 0{\cdot}02$). Greater vigilance is required in the investigation of patients presenting with iron-deficiency anaemia.

Delays in the diagnosis or treatment of patients with carcinoma of the colon are more common with right-sided malignancy[1]. The clinical significance of such delay is uncertain and the outcome may be worse, better or no different from that of left-sided tumours[2–5].

This study examined incidence of delays in the treatment of patients with right-sided colonic cancer, reasons for the delay and effects on survival. Treatment of patients with colonic malignancy may be influenced by a number of variables, including speed of presentation to the general practitioner (GP) and subsequent referral to hospital, speed of diagnosis and any administrative delays affecting the admission when a diagnosis has been established. Average reported delays in the treatment of colonic cancer[1,6–8] range from 17 to 31 weeks but a significant proportion of patients are treated within 12 weeks of the onset of symptoms[9]. For the purpose of this study, 12 weeks was therefore accepted as the 'gold standard'.

Patients and methods

Case records were studied for 152 consecutive patients with carcinoma of the right colon admitted to a single surgical unit between 1979 and 1989. All patients had invasive adenocarcinoma of the colon arising proximal to the splenic flexure.

Two groups of patients were identified: group 1 comprised 91 patients undergoing treatment within 12 weeks of the onset of symptoms and group 2 61 patients who suffered varying degrees of delay. The mean (95 per cent confidence interval) time between the onset of symptoms and definitive treatment of carcinoma was 9·4 (8·1–10·7) weeks in group 1 and 48·1 (38·9–57·3) weeks in group 2.

Group 1 included 16 patients presenting with acute intestinal obstruction. Previous studies have shown that such patients have a short history and a poor prognosis[10,11]. Patients with obstruction were therefore excluded from this study.

Information was obtained concerning delays in treatment, clinicopathological variables and patient survival. Patients were followed for a minimum of 5 years after surgery. Information concerning survival was obtained from GPs when patients defaulted from follow-up. Two patients who left the area and were lost to follow-up have been presumed dead for statistical analysis. The median duration of follow-up was 60 (range 28–96) months. Survival was measured by life-table methodology[12,13] and the log rank test[14] used in the statistical analysis. Other clinical variables in subgroups of patients were compared by χ^2 analysis and Fisher's exact test.

Results

Causes of delay

Three identifiable causes of delayed treatment were found in group 2; ten patients had more than one source of delay. Late presentation to the GP occurred in 17 patients. Treatment was delayed by the practitioner in 18 patients, the most common error being failure to initiate investigation of iron-deficiency anaemia (16 patients). In 36 patients delay resulted from failure of hospital clinicians to diagnose colonic carcinoma. In 17 of these, iron-deficiency anaemia was not investigated or incorrectly attributed to an alternative benign disease such as peptic oesophagitis or duodenal ulceration. The patients presented in various hospital departments and the anaemia was usually an incidental finding during treatment of another illness. Review of the records showed that an authentic alternative cause of anaemia was proven in only three of the 17 patients (peptic oesophagitis in two, gastric leiomyoma in one).

Investigations performed by hospital clinicians included double- or single-contrast barium enema (102 patients), barium follow-through (11), barium meal or gastroscopy (49) and colonoscopy (19). In 19 patients the diagnosis was missed despite appropriate investigations (double-contrast barium enema in 16 patients, colonoscopy in three). Failures of colonoscopy were attributable to inability to reach the ascending colon or caecum.

Administrative delays in treatment were negligible. All patients were admitted to hospital within 2 weeks when the diagnosis of colonic carcinoma was established.

Clinical presentation

There was a significantly different incidence of anaemia, defined as a haemoglobin concentration below 11 g/dl, in the two groups of patients. Fifty-one (84 per cent) of the patients in group 2 and 41 (55 per cent) of those in group 1 presented with anaemia ($\chi^2 = 12{\cdot}87$, 1 d.f., $P < 0{\cdot}001$).

Table 1 *Patient details and location of primary tumours*

	Group 1 ($n = 75$)	Group 2a ($n = 31$)	Group 2b ($n = 30$)
Sex ratio (M:F)	36:39	10:21	13:17
Mean (range) age (years)	69 (25–98)	71 (34–88)	68 (36–95)
Location of tumour			
Caecum	32 (43)	15 (48)	14 (47)
Ascending colon	13 (17)	6 (19)	1 (3)
Hepatic flexure	5 (7)	4 (13)	0 (0)
Transverse colon	20 (27)	5 (16)	12 (40)
Multiple sites	1 (1)	1 (3)	1 (3)
Not stated	4 (5)	0 (0)	2 (7)

Values in parentheses are percentages

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It was possible to identify two subgroups in group 2. Thirty-one patients (group 2a) presented with vague malaise and symptoms attributable to anaemia; these patients had no specific abdominal or bowel symptoms. Thirty patients (group 2b) had significant abdominal symptoms including pain, altered bowel habit, or awareness of an abdominal mass.

Comparison of groups 1, 2a and 2b (Table 1)

There was no significant difference between the groups with regard to age and sex. The location of the primary tumour was based on the description given by the operating surgeon; there was a significantly higher incidence of tumours arising at or proximal to the hepatic flexure in group 2a compared with group 2b ($\chi^2 = 5{\cdot}06$, 1 d.f., $P < 0{\cdot}05$).

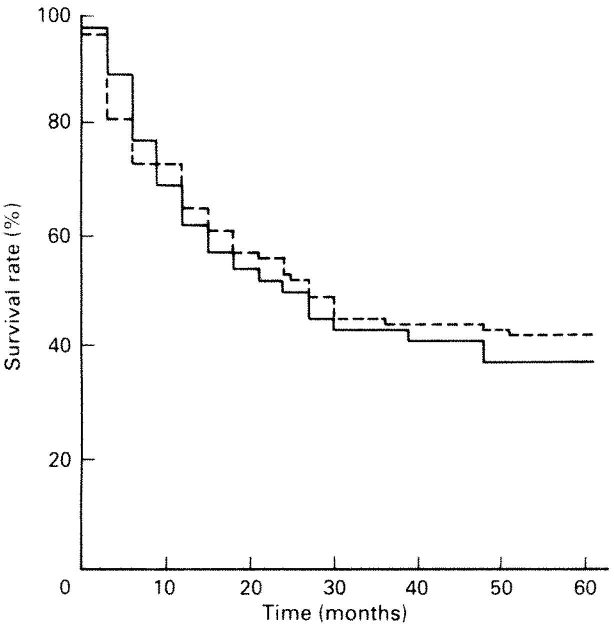
Treatment and hospital mortality (Table 2). There was no significant difference between the groups regarding the resectability of primary tumours and the incidence of palliative operations or hepatic metastases. The lower incidence of palliative procedures in group 2a was not statistically significant ($\chi^2 = 2{\cdot}21$, 1 d.f., $P > 0{\cdot}10$).

The incidence of perioperative blood transfusion and number of units of blood administered were similar in the three groups. For groups 1, 2a and 2b the proportions transfused were 77, 81 and 74 per cent respectively. The respective median (range) amounts transfused were 3 (2–12), 4 (2–12) and 3 (2–10) units.

Table 2 *Comparison of resection rates, palliative operations, hepatic metastases, hospital mortality and pathology*

	Group 1 ($n = 75$)	Group 2a ($n = 31$)	Group 2b ($n = 30$)
Primary tumour resected	72 (96)	31 (100)	27 (90)
Palliative operation	27 (36)	6 (19)	12 (40)
Hepatic metastases	13 (17)	4 (13)	6 (20)
Hospital death	3 (4)	0 (0)	2 (7)
Pathology (Dukes' stage)			
A	3 (4)	1 (3)	1 (3)
B	32 (43)	22 (71)	9 (30)
C	37 (49)	8 (26)	17 (57)
Not known	3 (4)	0 (0)	3 (10)

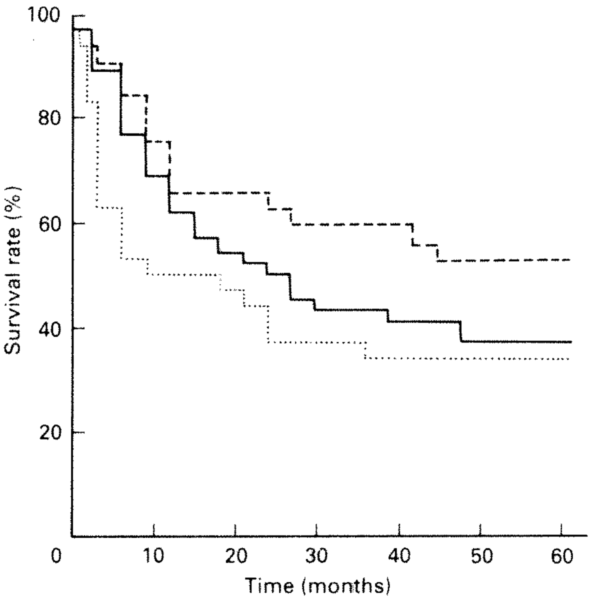
Values in parentheses are percentages



No. at risk

Group 1	64	55	46	42	35	35	33	30	26	25
Group 2	54	42	35	32	27	25	24	22	20	20

Figure 1 *Crude actuarial 5-year survival curves for patients in groups 1* (——) *and 2* (– – –)



No. at risk

Group 1	64	55	46	42	35	35	33	30	26	25
Group 2a	29	26	20	20	19	17	17	16	15	15
Group 2b	25	16	15	12	8	8	7	6	5	5

Figure 2 *Crude actuarial 5-year survival curves for patients in groups 1* (——), *2a* (– – –) *and 2b* (·····)

The 30-day hospital mortality rate was 4 per cent, with no significant difference between the groups. The causes of hospital death included pulmonary embolism (two patients), cardiac failure (two) and carcinomatosis (one).

Pathology (Table 2). There was a significantly lower incidence of Dukes' C tumours in group 2a compared with the other groups (group 2a *versus* group 2b: $\chi^2 = 6{\cdot}68$, 1 d.f., $P < 0{\cdot}01$; group 2a *versus* group 1: $\chi^2 = 4{\cdot}77$, 1 d.f., $P < 0{\cdot}05$).

Survival. For the crude 5-year survival curves, there was no significant difference between groups 1 and 2 (*Figure 1*). Analysis of the subgroups (*Figure 2*) revealed that patients in group 2a had a significantly higher survival rate than those in group 2b ($\chi^2 = 5{\cdot}73$, 1 d.f., $P < 0{\cdot}02$).

Discussion

Treatment of right-sided colonic cancer was delayed for more than 12 weeks in 40 per cent of the patients in this study. The factors involved in delay included late presentation to the GP, failure of the practitioner to investigate or refer the patient and failure of hospital clinicians to investigate or diagnose the illness. In a similar study, Fegiz *et al.*[5] found that 70 per cent of patients with carcinoma of the right colon suffered delays of more than 3 months, and Ratcliffe *et al.*[1] suggested that delayed presentation to the GP was the most common cause of delayed treatment of right-sided malignancies. It is probable that the relative contribution of patients, GPs and hospital clinicians in delayed treatment varies in different communities.

In the present study the most common error on the part of GPs was failure to determine the cause of iron-deficiency anaemia; this was also a frequent error during hospital management if the anaemia was an incidental finding during treatment of another illness. The association between iron-deficiency anaemia and occult carcinoma of the colon is well established[5–8,15–17], and it is surprising that this error persists.

There is a significant error rate in the diagnosis of right-sided colonic cancer by barium enema examination, false-negative results occurring in 7–26 per cent of patients[5,16]. The diagnosis of colonic cancer was missed in 16 of 102 patients undergoing barium enema examination in this study. Greater use of colonoscopy should reduce the incidence of diagnostic failure, although endoscopy failed for three patients in the present study.

Overall, the survival rate of patients who suffered delays in treatment was not significantly different from that of those who presented early. Previous studies have shown that there is a poor correlation between the duration of symptoms and the prognosis of colonic carcinoma[5,9,17]. The group of 61 patients suffering delays in diagnosis included two subgroups with very different prognoses. Patients presenting with anaemia and no abdominal symptoms had a relatively favourable prognosis. Thirty-one patients presented in this fashion and, despite delays in treatment, the 5-year survival rate of this group was higher than that of any other (*Figure 2*). The Dukes' stages of the tumours in this subgroup were more favourable; Fegiz *et al.*[5] have also noted that patients presenting with anaemia and no abdominal symptoms have a better prognosis. It appears that these tumours occur more often in the proximal part of the right colon (*Table 1*).

Would earlier diagnosis in patients with anaemia result in improved survival? It would appear that many of these patients have relatively slow-growing tumours with a low potential for spread. It is difficult to judge whether speedier diagnosis would improve the survival statistics. The incidence of error in diagnosis of carcinoma of the right colon is, however, a cause for concern and an important quality issue. GPs and hospital clinicians must exercise greater vigilance, particularly in the assessment of patients presenting with iron-deficiency anaemia. Such patients should receive a full investigation and clinicians should be aware of the potential errors in barium enema diagnosis of right-sided colonic malignancy.

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Colonoscopic surveillance after curative resection for colorectal cancer

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Colonoscopic surveillance after resection for colorectal cancer has been advocated to improve detection of anastomotic recurrence, and of synchronous and metachronous tumours. The benefit provided by colonoscopy remains unproven, and the best timing of examination is unclear. To determine the value of colonoscopy after curative resection for large bowel cancer, the efficacy of an endoscopic surveillance programme in the early detection of intraluminal bowel recurrence in a series of patients admitted with colorectal cancer was examined. Between April 1983 and December 1988, 132 patients underwent colonoscopy. Eight (6·1 per cent) were found to have intraluminal recurrence without evidence of extraluminal spread. Six of these recurrences were at the site of anastomosis and two represented metachronous tumour development. All of these patients were symptomatic at the time of diagnosis. In 15 patients (11·4 per cent), adenomatous polyps were discovered during the initial endoscopic examination. These results indicate that colonoscopic surveillance will rarely allow early detection of asymptomatic intraluminal bowel recurrence, but is valuable in the detection of synchronous lesions. Frequent surveillance is not justified in the early postoperative years and colonoscopy should probably be confined to a single procedure to exclude synchronous lesions.

Approximately 60 per cent of patients with colorectal cancer undergo potentially curative surgery[1]. Some 50 per cent of these patients will die in the ensuing 5 years, the vast majority from recurrence of disease[2]. The prognosis for patients with colorectal cancer is directly related to the stage of disease at the time of diagnosis[3]. Similarly, successful resection of recurrent and metachronous tumour is directly related to early detection[4]. Thus, it is generally believed that early detection and management of recurrence after curative resection can prolong life. For this reason it is argued that some form of follow-up is indicated for the remainder of the patient's life, with the aim of early detection of recurrence. As part of a detailed surveillance programme, colonoscopy has been advocated as a valuable method for detecting synchronous lesions and intraluminal recurrence[5–7], with better results than barium enema[8]. In common with other conditions for which colonoscopic surveillance has been advocated, such as adenomatous polyposis and long-standing colitis, the optimal timing of colonoscopic follow-up and its value in reducing mortality rates from development of cancer or recurrent disease remain in doubt[9,10]. Postoperative endoscopic surveillance might be expected to allow early diagnosis of anastomotic recurrence in addition to excluding synchronous or metachronous tumours. As the majority of anastomotic tumours occur within 2 years of surgery, intensive colonoscopic follow-up has been advocated during this period.

This study assessed prospectively the efficacy of an intensive surveillance programme over a 5-year period in a large series of patients with colorectal cancer. The aims of the study were to determine the value of intensive colonoscopic surveillance in the early detection of locally recurrent bowel carcinoma in patients who have undergone curative resection for colorectal cancer, and to determine the numbers of synchronous and metachronous tumours detected during this period.

Patients and methods

Between April 1983 and December 1988, 441 patients were admitted to this hospital with a diagnosis of colorectal cancer. Of these, 325 (73·7 per cent) underwent a potentially curative operation and were followed prospectively. Of the 325 patients, 132 (40·6 per cent) were enrolled into a strict endoscopic surveillance programme. Allocation to surveillance was not random but was based on the operating policy of the clinician responsible.

Patients on the surveillance programme underwent total colonoscopy after operation and subsequently at 6, 12, 18, 30 and 48 months. All patients also had a complete physical examination with measurement of the haemoglobin level and liver biochemistry. A detailed history of relevant symptoms such as abdominal pain, weight loss, bleeding or altered bowel habit was obtained at each visit. Particular care was taken to determine whether the symptoms had urged earlier presentation or whether the examination was purely part of the surveillance exercise. All positive findings at colonoscopy were carefully recorded, including the presence of adenomatous polyps and metachronous tumours. Data regarding age, sex, tumour stage and differentiation are given in *Table 1*.

Follow-up was complete in all 132 patients. The date and cause of all deaths were obtained from hospital records, or though direct contact with the general practitioner. The mean follow-up was 5·5 (range 3·2–8·8) years.

Table 1 *Details of patients*

Median (range) age (years)	63·5 (35–84)
Sex ratio (M:F)*	78:54 (59:41)
Dukes' stage*	
A	23 (17)
B	72 (55)
C	37 (28)
Tumour grade*	
Poorly differentiated	9 (7)
Moderately differentiated	118 (89)
Well differentiated	5 (4)

*Values in parentheses are percentages

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Table 2 *Details of original disease in patients with tumour recurrence*

Patient no.	Age (years)	Sex	Site of original tumour	Initial operation	Dukes' stage	Time to recurrence (months)
12	78	M	Sigmoid colon	Left hemicolectomy	B	8·6
105	78	M	Rectum	Anterior resection	B	43·2
110	67	M	Rectum	Anterior resection	B	28·3
153	66	F	Sigmoid colon	Anterior resection	C	9·7
200	80	F	Ascending colon	Right hemicolectomy	C	22·1
310	81	F	Transverse colon	Right hemicolectomy	B	13·4
312	59	M	Rectum	Anterior resection	C	10·3
369	59	M	Rectum	Anterior resection	B	7·0

Results

At colonoscopy eight patients (6·1 per cent) were found to have recurrent cancer without evidence of extracolonic spread (*Table 2*). Six of these cancers were situated at the anastomosis; the remaining two were metachronous tumours, giving a metachronous tumour rate of 1·5 per cent. All eight patients were symptomatic at the time of follow-up colonoscopy. Three patients presented with altered bowel habit, three with rectal bleeding, one with fatigue related to anaemia and one with abdominal pain. Four patients underwent a second potentially curative procedure, three of whom are alive at least 3 years after the second operation.

Twenty-two benign adenomatous polyps were discovered endoscopically in 15 patients (11·4 per cent) over the study period. None of these patients underwent total colonoscopy before operation and all were asymptomatic at the time of diagnosis. In 14 of the 15 patients polyps were discovered at the first endoscopic examination after surgery. In one case a benign adenoma was discovered endoscopically 6 months after the initial normal examination.

Discussion

The optimum management of patients who have had successful resection for large bowel cancer remains in doubt. Several workers have recommended intensive screening programmes combining faecal occult blood testing, monitoring of carcinoembryonic antigen levels, computed tomography and colonoscopic examination in an effort to detect extraluminal and intraluminal recurrence at an early and curable stage[9,11–13]. Colonoscopy seems to be the most appropriate technique for the early detection of intraluminal recurrence; however, data regarding the precise benefit of intensive surveillance programmes and the frequency and timing of endoscopy are not currently available. By prospectively following a large group of patients enrolled in an intensive endoscopic surveillance programme, the present study attempted to answer some of these questions.

The results indicate that colonoscopic follow-up has little part to play in the early detection of anastomotic recurrence in asymptomatic individuals. The intraluminal recurrence rate of 6·1 per cent in this series is similar to those reported by others[7,14]. However, true asymptomatic intraluminal recurrence was not observed in the present study as, in all cases, symptoms rather than routine surveillance prompted a search for recurrent malignancy. This is in common with surveillance studies of long-standing colitis[15].

The four patients (3·0 per cent) in the present study who underwent a second potentially curative procedure, three of whom are alive at the time of writing, cannot be claimed to have benefited from colonoscopy. The failure to detect true asymptomatic bowel recurrence is consistent with the belief that most intraluminal recurrence begins in the extraluminal tissue and only secondarily invades the bowel wall[16]. The present findings agree with those of Cochrane *et al.*[11], and indicate that awareness and early investigation of symptoms is more appropriate than routine endoscopy of asymptomatic individuals.

The finding of adenomatous polyps in approximately 11 per cent of patients at the first postoperative colonoscopic examination confirms the view that synchronous neoplasms are commonly associated with colorectal cancer[17–19]. In the present series, however, these polyps were effectively cleared by the first postoperative procedure. (The single polyp found 6 months later at the time of follow-up endoscopy may well represent a 'missed' synchronous lesion rather than a metachronous neoplasm.)

This study indicates that an intensive colonoscopic surveillance programme after curative surgery for colorectal cancer does not result in earlier diagnosis of intraluminal bowel recurrence and therefore will not offer substantial benefit to the patient. The relative frequency of synchronous lesions confirms the importance of examining the whole colon either before or soon after operation to allow diagnosis of synchronous cancer and removal of adenomas. Further colonoscopy in the early postoperative years may safely be confined to symptomatic patients.

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Surgical workshop

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Visualization of the ureter during laparoscopic colonic resection

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The growing enthusiasm for laparoscopic surgery following the success of laparoscopic cholecystectomy has led many surgeons to use this technique for colonic resection. In either right- or left-sided open colonic resection, a critical phase of the operation is to visualize the ureter clearly to avoid iatrogenic trauma. Using the laparoscopic technique, the absence of tactile sensation and the limited field of view make it more difficult to see the ureter throughout its entire course. This identification is especially problematic (though all the more important) in the presence of inflammation or tumour, as the normal anatomical position of the ureter may be distorted.

Surgical technique

Before commencing the laparoscopic operation, cystoscopy is performed and an illuminated 6-Fr ureteric probe (Karl Storz, Culver City, California, USA) 75 cm long (*Figure 1*) is inserted into the ureter on the same side as the colonic lesion. The probe is connected to a xenon light source by a screw fitting, and the laparoscopy is begun. When the colon has been elevated, the light source is turned on and the laparoscope source turned down. By this manoeuvre the surgeon is able to see the illuminated ureter in its entirety shining through the retroperitoneal structures. The procedure helps to localize this important structure while dissection of the lateral aspect of the colonic mesentery proceeds. Obviously this method is an adjunct to careful dissection, and it merely helps to ensure that the operation is completed safely.

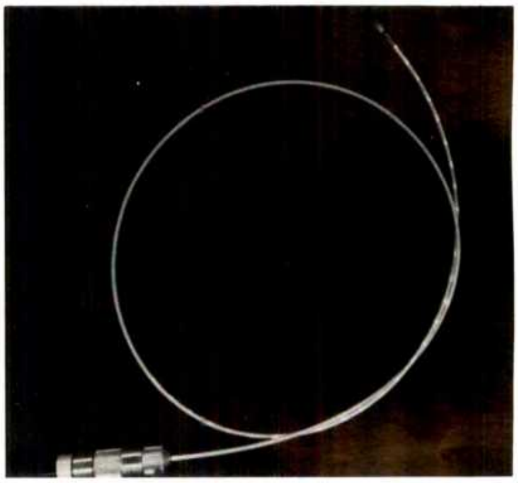

Figure 1 *The illuminated 6-Fr ureteric probe*

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Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma

Swedish Rectal Cancer Trial

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Between March 1987 and February 1990, 1168 patients with resectable rectal cancer were recruited into a nationwide Swedish trial. Patients were randomly allocated to receive either preoperative irradiation (25 Gy in five fractions over 1 week) followed by surgery within 1 week, or surgery alone. In each group 454 patients underwent curative surgery. The groups were well matched for age, sex and surgical procedure. The postoperative mortality rates did not differ: 4 per cent after irradiation versus *3 per cent after surgery alone, but the postoperative mortality rate was significantly higher in patients treated with a two- rather than three- or four-portal technique (15* versus *3 per cent,* $P < 0{\cdot}001$*). More perineal wound infections were found in patients receiving irradiation (20* versus *10 per cent,* $P < 0{\cdot}001$*). No difference in the incidence of anastomotic dehiscence or other postoperative complication was found between the groups. Preoperative radiotherapy with a short-term high-dose technique can be delivered without major acute adverse effects, provided the irradiation technique is optimized.*

Irradiation as adjuvant treatment for patients with rectal cancer can be used before[1–4] and after[5–8] operation. Reduction of the local recurrence rate has usually been more pronounced after preoperative than postoperative treatment[9]. Meta-analysis, including all trials published before 1986, indicated a marginally positive effect on survival if radiotherapy was given (4·3 per cent)[10]. Most studies in this meta-analysis used low radiation doses unlikely to destroy micrometastases[11]. None of the more recent trials, in which significant reductions in local recurrence rate have been noted, was included in the analysis.

It is not uniformly accepted that preoperative radiotherapy can be delivered without a major negative influence on the outcome of subsequent surgery. This trial was initiated to explore whether short-term high-dose preoperative irradiation given with an optimized technique to patients aged 79 years or less with resectable rectal carcinoma could reduce the incidence of local recurrence without increasing the postoperative mortality rate, and increase the long-term survival. This initial report describes the trial design, patient characteristics and surgical outcome, focusing on the immediate postoperative effects of treatment.

Patients and methods

Randomization

Randomization in blocks of four or six patients was carried out by telephone to the six different Swedish regional oncological centres. The numbers in the blocks were unknown to the investigators. Patients were stratified for hospital and randomly allocated to receive preoperative irradiation for 1 week followed by surgery within the next week, or surgery with no additional radiotherapy or other anticancer treatment until recurrence occurred.

Sample size

To reduce the local recurrence rate from 20 to 10 per cent, 475 patients had to be recruited to detect the difference with 90 per cent probability and a 5 per cent significance level. To detect an increase in postoperative mortality rate from 2 to 5 per cent, 750 patients had to be included (90 per cent probability, 5 per cent significance level). To show an increase in survival rate of 10 per cent (from 50 to 60 per cent) after 5 years with 80 per cent probability and a 5 per cent significance level, 750 patients undergoing curative resection had to be recruited. Allowing for a 10 per cent drop-out rate, and that approximately 20 per cent of patients would have generalized disease at surgery or undergo locally non-curative resection, at least 1100 patients had to be included.

Patients

Between March 1987 and February 1990, 1168 patients with resectable rectal carcinoma in whom an abdominal procedure was planned were recruited into the trial.

Inclusion criteria were: histopathologically proven adenocarcinoma; tumour situated below the sacral promontory as shown on a side projection on barium enema; age 79 years or younger; and informed consent with approval of the local ethical committee. Exclusion criteria were: locally irresectable tumour; patients with a small tumour, in whom local surgical treatment was intended; known generalized disease; previous radiotherapy to the pelvis; and other malignant disease, except squamous cell carcinoma of the skin.

Twenty-one patients were excluded because they did not fulfil the inclusion criteria, leaving 1147 correctly assigned (*Table 1*). The sex and age distributions were similar in the two groups. The median (range) age in the group receiving irradiation was 69 (27–79) years for women and 68 (31–79) years for men. The corresponding figures for patients given surgery alone were 67 (31–79) and 67 (33–79) years. The type of surgery performed in each group is shown in *Table 2*.

Irradiation technique

The target volume included the anal canal, the primary tumour, the mesorectal and presacral nodes, the lymph nodes along the internal

Table 1 *Study cohort*

	Irradiation		Surgery alone	
Randomized		583		585
Ineligible	10		11	
Eligible		573		574
Refused surgery	1		0	
No resection	19		17	
Local resection		553		557
Distant metastases	42		41	
Locally non-curative	14		19	
Local cure uncertain	43		43	
Patients treated curatively		454		454

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Table 2 *Type of surgery according to randomization group*

	Irradiation						Surgery alone					
	Locally curative		Local cure uncertain		Locally non-curative		Locally curative		Local cure uncertain		Locally non-curative	
Distant metastases	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Anterior resection	206	15	10	2	6	4	194	13	12	2	3	3
Abdominoperineal resection	243	10	33	5	8	5	256	10	31	5	16	4
Hartmann's procedure	4	0	0	0	0	1	3	1	0	0	0	3
Proctocolectomy	1	0	0	0	0	0	1	0	0	0	0	0
Total	454	25	43	7	14	10	454	24	43	7	19	10

Patients not undergoing resection are excluded

Table 3 *Type of surgery according to local Dukes' stage and distant metastases*

	Irradiation						Surgery alone					
	Stage A		Stage B		Stage C		Stage A		Stage B		Stage C	
Distant metastases	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Anterior resection	70	2	83	4	69	15	60	2	68	6	81	10
Abdominoperineal resection	106	3	98	7	80	10	89	2	90	5	124	12
Hartmann's resection	0	0	3	0	1	1	1	0	2	1	0	3
Proctocolectomy	0	0	0	0	1	0	0	0	1	0	0	0
Total	176	5	184	11	151	26	150	4	161	12	205	25

Patients not undergoing resection are excluded

Table 4 *Postoperative hospital mortality according to age and curative surgery*

	Irradiation				Surgery alone			
	Curative		Non-curative		Curative		Non-curative	
Age (years)	Total	Deaths	Total	Deaths	Total	Deaths	Total	Deaths
≤49	20	0 (0)	7	0 (0)	28	0 (0)	10	0 (0)
50–54	21	1 (5)	12	0 (0)	30	0 (0)	15	2 (13)
55–59	48	1 (2)	11	0 (0)	40	0 (0)	15	0 (0)
60–64	69	1 (1)	20	1 (5)	68	1 (1)	20	1 (5)
65–69	99	1 (1)	29	3 (10)	91	1 (1)	22	1 (5)
70–74	116	6 (5)	17	3 (18)	112	2 (2)	21	3 (14)
75–79	81	2 (2)	22	3 (14)	85	2 (2)	17	2 (12)
Total	454	12 (3)	118	10 (8)	454	6 (1)	120	9 (8)

Values in parentheses are percentages

Table 5 *Postoperative hospital mortality according to surgical procedure*

	Irradiation		Surgery alone		Total	
	Total	Deaths	Total	Deaths	Total	Deaths
Anterior resection	243	6 (2)	227	5 (2)	470	11 (2)
Abdominoperineal resection	304	14 (5)	322	7 (2)	626	21 (3)
Hartmann's resection	5	0 (0)	7	1 (14)	12	1 (8)
Proctocolectomy	1	0 (0)	1	0 (0)	2	0 (0)
No resection	19	2 (11)	17	2 (12)	36	4 (11)
Refused surgery	1	0 (0)	0	0 (0)	1	0 (0)
Total	573	22 (4)	574	15 (3)	1147	37 (3)

Values in parentheses are percentages

iliac artery, the lumbar lymph nodes up to the level of the upper border of the fifth lumbar vertebra and the lymph nodes at the obturator foramen. The treatment was delivered with three portals as previously described[12] with the patient in a prone position, or with a four-portal 'box' technique with the patient lying supine.

The protocol tumour dose was 25 Gy in five fractions over 1 week. The treatment was individually planned in each patient and given with 5–16-MV photons. The dose was defined at the intersection of the central axes of the three or four beams. The protocol recommended a treatment time from Monday to Friday giving a cumulative radiation effect (CRE) value of 15·1. Treatment started on other days resulted in a slightly lower CRE of 14·5. The CRE was calculated according to Kirk *et al.*[13] with correction for late effects as described by Turesson[14].

Surgery and histopathology

Standard surgical procedures were used with the choice of anterior resection or abdominoperineal excision determined by the surgeon. A procedure was considered locally curative if the surgeon and histopathologist reported free margins, even if the bowel was perforated at surgery. Locally uncertain curative surgery was defined as either the surgeon or pathologist reporting a questionable margin. In all other cases, the treatment was reported as locally non-curative.

Postoperative mortality was calculated as death in hospital and that within 30 days, facilitating comparison with other reports. Complications of surgery were prospectively assembled and registered.

Resection specimens were examined by a local pathologist and the tumour classified according to Dukes' original staging system. The number of examined and tumour-infiltrated lymph nodes were recorded, and the pathologist classified the resection as locally curative, uncertain curative or locally non-curative.

Surgery was considered curative when there were no distant metastases and the resection was locally curative.

Statistical analysis

Differences in proportions were assessed using χ^2 analysis and differences between means with Student's t test, with a significance level of $P < 0{\cdot}05$. Analyses of postoperative mortality rates were based on all eligible patients, whereas postoperative morbidity was analysed only in those who underwent resection. All comparisons between treatment groups were on the basis of intention to treat.

Table 6 *Recorded causes of postoperative hospital death*

	Irradiation	Surgery alone
Heart failure	9	8
Pulmonary embolism	3	2
Infectious complication	4	0
Anastomotic dehiscence	3	1
Small bowel obstruction	1	0
Cancer	1	3
Surgical mishap	1	1
Total	22	15

Results

Radiotherapy

Seventeen patients (3 per cent) had no radiotherapy although they were allocated to that treatment group, and five patients (1 per cent) received less than 25 Gy. Radiotherapy started on a Monday (i.e. was delivered over 5 consecutive days) for 424 patients and was delivered over 7 days in 102. Only 29 patients (5 per cent) had a treatment period longer than 7 days. The operation was performed within 3 days in 202 patients (36 per cent), after 4–7 days in 287 (52 per cent), after 8–14 days in 36 (7 per cent) and later than 15 days in 30 (5 per cent). Treatment was given with a three- or four-portal technique in 175 and 332 patients respectively. Forty-eight patients were irradiated with a two-portal technique using one frontal and one dorsal portal. Most patients experienced no adverse effects during irradiation but some had bilateral pain in the buttocks. This effect was reversible in all but one patient, who had persistent pain for more than 2 years.

Surgery and histopathology

Table 3 shows the local stage according to surgical procedure. A difference in Dukes' stage between the two treatment groups was found ($\chi^2 = 11{\cdot}8$, 3 d.f., $P = 0{\cdot}008$). The distribution of distant metastases was similar in the two groups (*Table 1*), giving 454 patients treated curatively in each group.

Postoperative mortality

The hospital mortality rate was 3 per cent for patients receiving surgery alone and 4 per cent for those given irradiation ($P = 0{\cdot}31$). The corresponding 30-day mortality rates were 2 and 2 per cent respectively. For patients randomized to irradiation, the hospital mortality rate was lower among those treated according to the protocol with three or four portals (3 per cent) than in those treated with a two-portal technique (15 per cent, $P < 0{\cdot}001$) or no irradiation (12 per cent, $P = 0{\cdot}13$). There was no significant difference in postoperative mortality rate between treatment with three *versus* four portals (3 *versus* 2 per cent, $P = 0{\cdot}98$).

The postoperative mortality rate increased with age, particularly for patients undergoing non-curative surgery (*Table 4*). Data on postoperative mortality with respect to surgical procedure are given in *Table 5*. Sex, time from irradiation to surgery and radiation energy ($\leqslant 8$ or > 8 MV) did not influence the postoperative mortality rate. The causes of death are given in *Table 6*.

Postoperative morbidity

Of the patients receiving irradiation followed by anterior or abdominoperineal resection, 56 per cent had no complications of surgery (*Table 7*). This figure was 66 per cent for patients receiving surgery alone ($P = 0{\cdot}001$). The difference was caused by an increased number of perineal wound infections after

Table 7 *Postoperative complications according to surgical procedure*

	Irradiation		Surgery alone	
	Anterior resection	Abdominoperineal resection	Anterior resection	Abdominoperineal resection
No complication	160 (66)	152 (50)	165 (73)	202 (61)
Wound infection	12 (5)	13 (4)	9 (4)	19 (6)
Perineal wound infection	0 (0)	63 (20)	0 (0)	29 (10)
Septicaemia	3 (1)	5 (2)	6 (3)	5 (2)
Anastomotic dehiscence	26 (11)	0 (0)	17 (8)	0 (0)
Wound rupture	8 (3)	12 (4)	5 (2)	7 (2)
Postoperative ileus	9 (4)	18 (6)	3 (1)	17 (6)
Miscellaneous	40 (16)	77 (25)	32 (14)	64 (20)

Values in parentheses are percentages

Table 8 *Hospital stay according to surgical procedure*

	Irradiation		Surgery alone		
	No.	Stay (days)*	No.	Stay (days)*	P†
Anterior resection	237	19 (7–79)	222	17 (7–65)	0·3
Abdominoperineal resection	289	25 (8–121)	315	21 (7–101)	<0·001
Hartmann's resection	5	29 (10–42)	6	24 (12–46)	0·9
Proctocolectomy	1	51	1	18	
No resection	17	23 (7–106)	15	21 (14–90)	0·03
Total	549	22 (7–121)	559	19 (7–101)	<0·001

*Values are mean (range). †Student's t test

abdominoperineal resection in patients given radiotherapy (20 *versus* 10 per cent for surgery alone, $P < 0{\cdot}001$). Of patients receiving irradiation, 11 per cent developed anastomotic dehiscence; the corresponding value for those undergoing surgery alone was 8 per cent ($P = 0{\cdot}3$). No differences in complication rates were detected if two, three or four portals were used, nor using different energies (≤ 8 or >8 MV).

Postoperative hospital stay

The mean (range) hospitalization time for patients undergoing surgery alone was 19 (7–101) days compared with 22 (7–121) days for those given irradiation ($P < 0{\cdot}001$) (*Table 8*). This difference was found mainly in those operated on with abdominoperineal resection ($P < 0{\cdot}001$); no significant difference was seen for patients treated by anterior resection. The mean postoperative stay in those undergoing abdominoperineal resection who had a perineal wound infection was 31 days after irradiation and 30 days after surgery alone ($P = 0{\cdot}7$). The corresponding figures for those without perineal wound infection were 24 and 20 days respectively ($P < 0{\cdot}001$). There was also a difference in hospital stay for those operated on with an exploratory laparotomy ($P < 0{\cdot}05$).

Discussion

In one Swedish trial[2], the short-term high-dose preoperative radiation regimen used in the present study reduced the proportion of local recurrences, and in another Swedish trial[9] it decreased this proportion to the same extent as high-dose postoperative radiotherapy. In neither trial was survival significantly influenced. There has, however, been some concern regarding acute adverse effects of the radiation regimen used in the present study. A significantly increased postoperative mortality rate was found in the Stockholm–Malmö trial[2], but not in the Uppsala study[9], using the same irradiation dose. The reasons for this difference may relate to the different irradiation techniques used. In the Stockholm–Malmö trial one dorsal and one frontal portal were used, with the patient in the supine position. In the Uppsala study, three dorsal portals were employed, with the patient in the prone position. The use of three or more portals considerably reduces the risk of surrounding organs not containing tumour cells obtaining the high radiation dose prescribed for the tumour target. Most patients died from cardiovascular disease rather than from infectious complications or causes immediately related to the irradiated area. These findings could indicate that irradiation of a large abdominal volume using a relatively high dose followed by immediate surgery might be detrimental, particularly to elderly patients.

In the present trial, patients irradiated as intended, with three or four portals, showed no increase in postoperative mortality rate over those receiving only surgery (3 per cent in both groups). In the minor proportion of patients not irradiated according to recommendations in the protocol, i.e. using the two-portal technique as in the Stockholm–Malmö trial, a high postoperative mortality rate of 15 per cent was noted. These results support the concept that a large irradiated volume may be detrimental. The follow-up is too short to evaluate late adverse effects, but none was found in an evaluation of patients treated with preoperative irradiation in the Uppsala trial[15].

In the present trial, as in others[1–3,9], the number of perineal wound infections increased for abdominoperineal resection with preoperative radiotherapy. There were no other differences in complication rate except a slightly prolonged hospital stay after surgery for patients given preoperative radiotherapy.

This study demonstrates that preoperative radiotherapy to a relatively high dose can be delivered with no major early adverse effects. The results indicate that the technique must be optimized so that unnecessarily large volumes are not irradiated, otherwise detrimental effects might outweigh possible benefits.

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In vitro response of the human anal canal longitudinal muscle layer to cholinergic and adrenergic stimulation: evidence of sphincter specialization

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A study was performed to determine the in vitro *response of the longitudinal smooth muscle layer (conjoined longitudinal coat) of the human anal canal to cholinergic and adrenergic stimulation, and to compare this with similar features of the internal anal sphincter (IAS) and rectal smooth muscle. Tissue was obtained from abdominoperineal and anterior resection specimens, and strips of muscle mounted for isometric tension recording in superfusion organ baths. Both conjoined longitudinal coat and IAS strips generated and maintained spontaneous myogenic tension (mean(s.e.m.) 0·10(0·01) and 0·48(0·04) g per mg tissue respectively), whereas equivalent rectal smooth muscle did not. Stimulation of muscarinic (cholinergic) receptors caused contraction of strips from the conjoined longitudinal coat and rectal smooth muscle layers in a dose-dependent manner (10^{-7}–10^{-4} mol/l); however, IAS strips relaxed (10^{-6}–10^{-4} mol/l). Activation of α-adrenergic receptors in conjoined longitudinal coat and IAS strips produced concentration-dependent contraction (10^{-7}–10^{-4} mol/l). In comparison, rectal smooth muscle relaxed. All muscle layers relaxed in response to β-adrenoceptor stimulation. These data indicate that in the anal canal both the conjoined longitudinal coat and IAS are specialized sphincteric smooth muscles.*

There are two predominant smooth muscle structures within the anal canal: the internal anal sphincter (IAS) and the conjoined longitudinal coat. The anatomy of these structures has been described previously and is well reviewed[1,2]. The IAS is the terminal part of the circular smooth layer of the gastrointestinal tract and consists of fascicles of smooth muscle fibres ensheathed in connective tissue. The conjoined longitudinal coat, on the other hand, is the most caudal extension of the longitudinal muscle layer of the gut and consists of much less smooth muscle than the internal sphincter. At the pelvic floor, the conjoined longitudinal coat is joined by some (scant) striated muscle fibres from the levator ani (pubococcygeus) and then traverses the anal canal between the internal and external sphincters. As it descends, it becomes progressively fibroelastic and gives off several septa which ramify through both the IAS and the lowermost part of the external sphincter, to gain attachment to the dermis of the anal and circumanal skin. In addition, other septa pass outward, away from the anal canal, to blend with the connective tissue of the ischiorectal fossa and perianal space.

Much is known about the activity of the IAS. It is recognized that it plays an important role in anorectal continence, being principally responsible for the generation and maintenance of resting anal canal pressure[3,4]. The IAS contracts spontaneously, developing a high degree of myogenic tone, and relaxes to allow the passage of stool, to permit anorectal sampling and in response to rectal distension. The conjoined longitudinal coat can now be imaged by endoanal ultrasonography and is seen during intersphincteric dissection of the anal canal but, compared with the IAS, little is known about its behaviour. Its true function is unknown; indeed, as far as the authors are aware, the activity of the human conjoined longitudinal coat has not been examined previously.

This paper describes studies in which aspects of the behaviour of the two smooth muscle layers of the anal canal were compared *in vitro*. In particular, their spontaneous activities and how these are modified by cholinergic and adrenergic drugs were examined. These agents were chosen to mimic the actions of important neurotransmitters in the gastrointestinal tract that are released from intrinsic enteric neurones as well as from extrinsic nerves of the sympathetic and parasympathetic nervous systems. To characterize the behaviour of anal canal smooth muscle further, similar experiments were also carried out on the equivalent muscle layers of the rectum.

Patients and methods

Sphincter tissue was obtained from patients undergoing abdominoperineal resection of the rectum and anal canal for low rectal carcinoma (three men, four women; median age 65 (range 62–75) years). Rectal smooth muscle was derived from this source and from patients with more proximal rectal tumours undergoing low anterior resection with coloanal anastomosis (four men; median age 63 (range 60–65) years). To maintain consistency in tissue collection, internal sphincter and conjoined longitudinal coat smooth muscle was obtained from adjacent sites in the anal canal, the most cranial part of which was defined by the attachment of the striated muscle of the pelvic floor. Rectal circular and longitudinal smooth muscle was acquired from the 'body' of the rectum, which was assumed to be midway along the craniocaudal axis of the resection specimen.

Once suitable tissue had been selected, the epithelium and submucosa were removed with the aid of a dissecting microscope. Adjacent strips containing parallel smooth muscle bundles were then excised, each measuring approximately 1 × 1 × 10 mm and weighing

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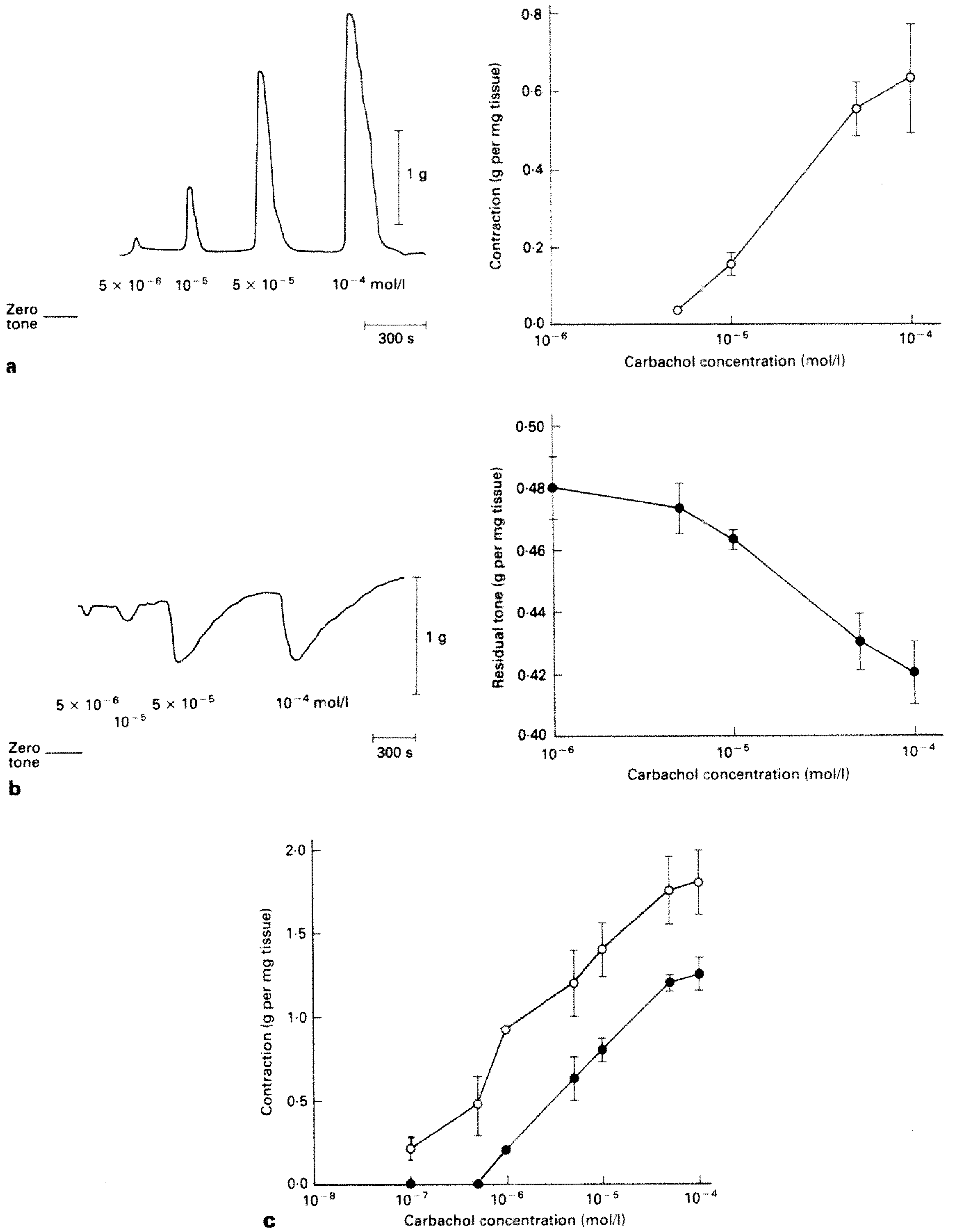

Figure 1 **a** *Response of smooth muscle strips from the conjoined longitudinal coat to increasing concentrations of carbachol, illustrated by a characteristic trace and a dose–response curve. Each point represents the mean(s.e.m.) of all strips tested* (n = *18*(*3*)). *Zero tone in this and subsequent figures represents the tension present in calcium-free solution.* **b** *Response of smooth muscle strips from the internal anal sphincter to increasing concentrations of carbachol, illustrated by a characteristic trace and a dose–response curve* (n = *30*(*6*)*; values are mean*(*s.e.m.*)). *Residual tone is the tension remaining in the strips after application of the drug.* **c** *Responses of longitudinal* (○) *and circular* (●) *smooth muscle strips from the rectum to increasing concentrations of carbachol* (n = *18*(*4*)*; values are mean*(*s.e.m.*))

5–8 mg. Threads were tied at each end of the strips, which were mounted for isometric tension recording in superfusion organ baths (capacity 0·2 ml). The strips were continuously superfused with Krebs solution (37°C) at a rate of 1 ml/min. Drugs and other agents being investigated were added to the Krebs solution before it was placed in the bath. The apparatus allowed six strips to be studied simultaneously. Tension was measured using Pioden transducers (Pioden Controls, Canterbury, UK) and recorded on a six-channel Teckman pen recorder (Teckman Electronics, Leamington Spa, UK). The strips were placed initially under 1·0 g resting tension and allowed to equilibrate for at least 1 h before the start of experiments. For calculation of spontaneous and stimulated tension, the tension present in strips held in calcium-free solution was regarded as the baseline (zero) and was subtracted from the observed tension.

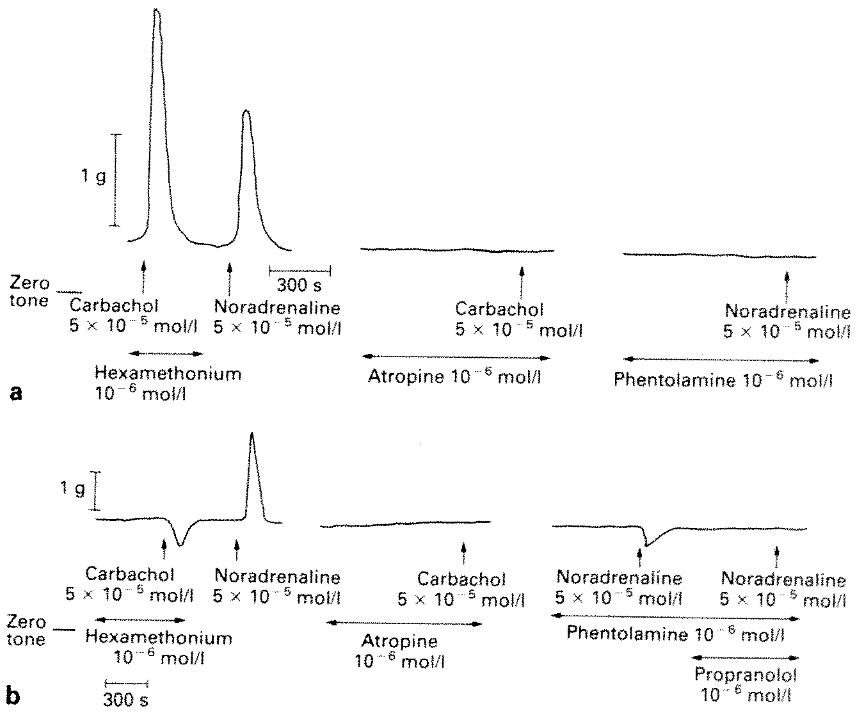

Figure 2 *Analysis of the actions of carbachol and noradrenaline on an isolated strip of human* **a** *conjoined longitudinal coat and* **b** *internal anal sphincter. Similar responses were seen in all strips tested* (n = *12(2)*)

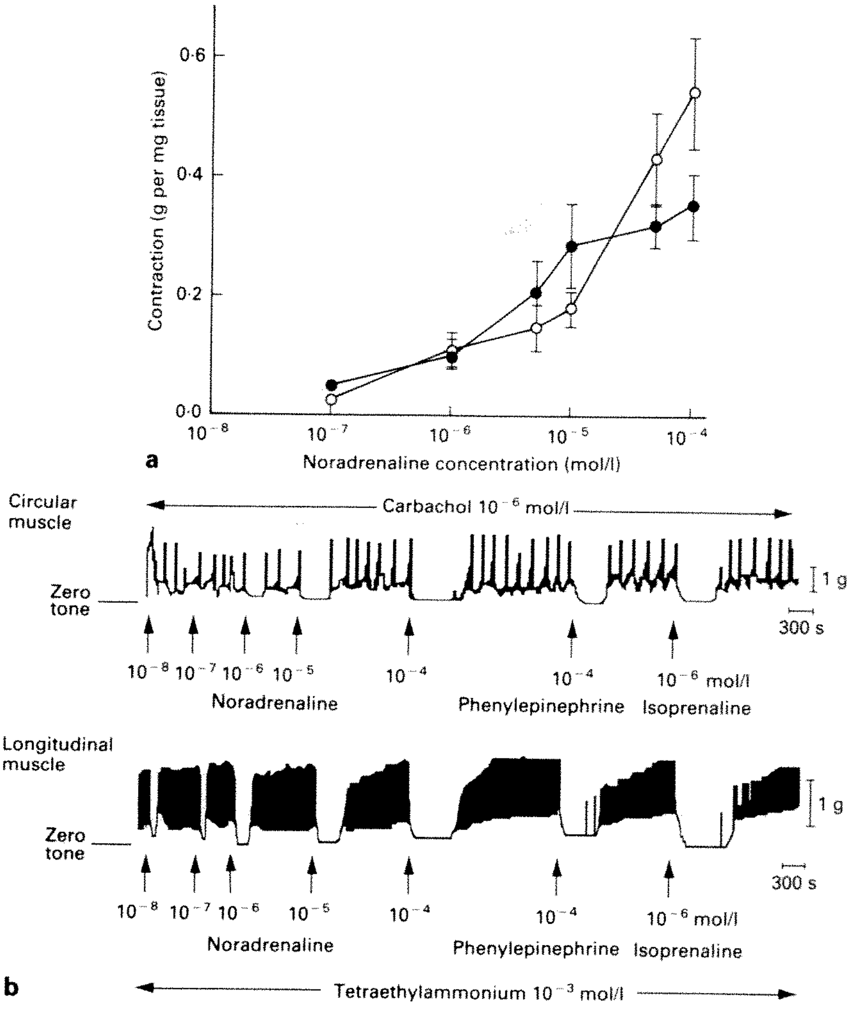

Figure 3 **a** *Response of the conjoined longitudinal coat* (n = *18(5)*; ○) *and internal anal sphincter* (n = *18(3)*; ●) *to increasing concentrations of noradrenaline. Values are mean(s.e.m.).* **b** *Response of the circular and longitudinal muscle layers of the rectum to increasing doses of noradrenaline, phenylephrine* (*an α-adrenoceptor agonist*) *and isoprenaline* (*a β-adrenoceptor agonist*). *Carbachol and tetraethylammonium were applied to increase basal tone and stimulate spontaneous activity, so revealing the inhibitory actions of the sympathomimetic agents. Similar responses were seen in all 12(2) preparations studied*

Standard Krebs solution was equilibrated with 97 per cent oxygen–3 per cent carbon dioxide. Drugs and agents used were: carbamylcholine chloride (carbachol); hexamethonium bromide; isoprenaline sulphate; phentolamine hydrochloride; phenylephrine hydrochloride; atropine sulphate; tetraethylammonium chloride; noradrenaline; propranolol hydrochloride; and tetrodotoxin.

Experimental results are expressed as mean(s.e.m.) and, where appropriate, statistical differences assessed with Student's unpaired t test. $P < 0{\cdot}05$ was considered significant. Numbers (n) are given in the form $x(y)$, where x is the number of strips and y the number of patients.

Results

Spontaneous tension

During the period of equilibration, muscle strips taken from the IAS contracted spontaneously and developed a mean(s.e.m.) steady-state tension of 0·48(0·04) g per mg tissue (n = 30(6)). By comparison, those from the conjoined longitudinal coat relaxed spontaneously and maintained a mean(s.e.m.) steady-state tension of only 0·10(0·01) g/mg (n = 24(5)). This difference was highly significant ($P < 0{\cdot}001$). In neither case did the nerve toxin tetrodotoxin (3×10^{-6} mol/l) reduce spontaneous tension, confirming that the effect was myogenic in origin. Both layers of smooth muscle from the rectum (n = 24(4)) completely relaxed in the organ baths and had no tension once the steady state was achieved (equal to that present in calcium-free solution).

Responses to cholinergic agonist

Carbachol is a cholinergic agonist; *Figure 1* shows the response of the various muscle strips to a 10-s application of this agent. Samples from the conjoined longitudinal coat (n = 18(3)) and both layers of the rectum (n = 18(4)) contracted in a dose-dependent manner on addition of carbachol, whereas those from the IAS relaxed (n = 30(6)). The responses were not modified by hexamethonium (10^{-6} mol/l) (n = 12(2)), a ganglionic (nicotinic) cholinergic receptor antagonist, but they were antagonized by atropine (10^{-6} mol/l) (n = 12(2)), which blocks the action of cholinergic agents at muscarinic (cholinergic) receptors (*Figure 2*).

Responses to adrenergic agonist

Noradrenaline is the principal neurotransmitter released by postganglionic sympathetic nerves. Its application to muscle strips from the conjoined longitudinal coat (n = 18(5)) and internal sphincter (n = 18(3)) for 20 s caused dose-dependent contractions (*Figure 3a*). In the presence of phentolamine, an α-adrenoceptor antagonist, the response of conjoined longitudinal coat strips to 5×10^{-5} mol/l noradrenaline was abolished (n = 12(2)); however, in the case of IAS strips, relaxation was revealed (n = 12(2)) (*Figure 2*). This modified internal sphincter response was abolished on addition of propranolol, a β-adrenoceptor antagonist (n = 6(2)). Both IAS and conjoined longitudinal coat strips relaxed in response to application of isoprenaline, a β-adrenergic agonist (10^{-9}–10^{-6} mol/l).

In their relaxed state, strips from neither layer of rectal smooth muscle responded to noradrenaline (n = 18(3)). If, however, tension and activity were raised by the addition of carbachol to circular strips (n = 12(2)) and tetraethylammonium to longitudinal strips (n = 12(2)), then noradrenaline was seen to have an inhibitory effect on both the frequency and amplitude of the resulting contractions. This inhibition could be reproduced by stimulation of both α- and β-adrenoceptors with phenylephrine or isoprenaline respectively (n = 12(2) for each layer; *Figure 3b*).

These results are summarized in *Table 1*.

Table 1 *Summary of results*

		Agonist effect	
	Tone	Cholinergic	α-Adrenergic
Internal anal sphincter	High	Relaxation	Contraction
Conjoined longitudinal coat	Low	Contraction	Contraction
Rectal smooth muscle	Absent	Contraction	Relaxation

Discussion

The importance of the smooth muscle components of the anal canal is becoming increasingly apparent[5] and a greater understanding of their properties will provide new insight into the mechanisms of continence and defaecation, and how they are altered to produce clinical syndromes such as anorectal incontinence. Such knowledge might also suggest novel ways in which sphincter activity can be altered pharmacologically.

Some aspects of human conjoined longitudinal coat and IAS muscle behaviour are similar. First, isolated strips from both layers generate and maintain spontaneous myogenic tension, although this is much less in the conjoined longitudinal coat. The mechanism responsible for this has been explored by Bouvier and Gonella[6]. Using the sucrose gap technique, they examined tension and electrical activity in circular and longitudinal muscle taken from the anal sphincter area of the cat. In the former they noted slow variations in smooth muscle membrane potential called slow waves. In longitudinal muscle, spike potentials were superimposed on these. Each slow wave (internal sphincter) or spike potential (conjoined longitudinal coat) was associated with an increase in basal tension. Both slow waves and tension disappeared in calcium-free solution and in the presence of manganese ions, indicating that electromechanical coupling was calcium dependent. Research is required to confirm whether human anal canal smooth muscle behaves in a similar fashion and also to elucidate further the processes responsible for spontaneous tone. This area is likely to be fertile ground for the pharmacological manipulation of sphincter activity in the future.

The conjoined longitudinal coat and IAS are also similar in their response to exogenous adrenergic agonists. Both contract when α-adrenoceptors are stimulated, but relax when β-adrenoceptors are stimulated. This behaviour is characteristic of sphincter-specialized gastrointestinal smooth muscle[7]. Non-sphincteric gastrointestinal smooth muscles, as evidenced by the response of both layers of rectum, relax when either of these receptors is stimulated[7]. The differences between responses of the circular smooth muscles of the anal canal and rectum have been described previously in the cat[8] and vervet monkey[9]. The mechanisms that underlie these differences in activity were not determined in the present study.

In its response to exogenous cholinergic agonists, the conjoined longitudinal coat contracts and so behaves like both layers of the rectum and smooth muscle elsewhere in the gastrointestinal tract[7]. The dose-dependent relaxation of the internal sphincter to muscarinic receptor activation is therefore outstanding, and currently not explained. It has been noted previously[10] and could result from a direct cholinergic effect on IAS smooth muscle. It is also conceivable, however, that cholinergic stimulation releases another agent that produces the ultimate mechanical response. Similar relaxations are seen in some vascular smooth muscle preparations, where they are thought to be mediated by the release of nitric oxide from endothelial cells[11,12]. Nitric oxide is a recently discovered endogenous bioactive substance with many functions[13–15], including that of an inhibitory neurotransmitter within the gastrointestinal tract[16]. As intrinsic nerves and small blood vessels are present in the muscle strips used in these studies, it is possible that nitric oxide mediates IAS relaxation in response to cholinoceptor stimulation. Further research is required to explore this phenomenon as it clearly has an important bearing on understanding of how enteric and parasympathetic cholinergic nerves interact with the internal sphincter.

Caution is required when interpreting the findings of *in vitro* experiments. However, on the basis of the present results, we believe that the conjoined longitudinal coat, like the IAS, shows true sphincter specialization both in its ability to generate spontaneous tension and in its pharmacological behaviour. No firm conclusions can be made about the function of the conjoined longitudinal coat, but the present findings are consistent with previous suggestions that it helps to maintain the structural integrity of the anal canal throughout the defaecation cycle, and contracts during the passage of faeces to shorten the anal canal and evert the anal margin[17,18]. *In vivo* as well as further *in vitro* experiments are required to confirm this suggestion and to explore the actions of the conjoined longitudinal coat more fully.

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Physiological and histochemical adaptation of the electrically stimulated gracilis muscle to neoanal sphincter function

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The physiological and histochemical characteristics of the gracilis muscle were studied in 19 patients undergoing electrically stimulated gracilis neosphincter construction. Indications for surgery were faecal incontinence (n = *11*) *and reconstruction following sphincter excision or congenital absence* (n = *8*). *Transposition of the gracilis muscle around the anal canal followed by chronic low-frequency electrical stimulation was associated with a shift in the frequency–response curve and a prolongation of the time-course of individual muscle twitches suggestive of transformation to a slow-twitch fatigue-resistant type. Temporary cessation of electrical stimulation resulted in a reversal of the frequency–response changes. Muscle biopsies taken before and a median of 80* (*range 49–137*) *days after transposition and low-frequency electrical stimulation indicated a significant increase in the proportion of type 1 fibres and a significant decrease in their diameter. These results show that the human gracilis muscle is capable of physiological and histochemical adaptation to long-term neosphincter function.*

Several skeletal muscle types have been used to augment or replace the anal sphincter musculature[1–5]. Pickrell *et al.*[3] first described the use of gracilis, which has subsequently become the muscle of choice for this purpose. The results have been unsatisfactory[6], at least in part because fast-twitch fatigable muscles have been used to perform a function normally carried out by those of slow-twitch fatigue-resistant type.

Recent advances in muscle physiology[7,8] have demonstrated in experimental animals that the properties of skeletal muscle may be modified by various stimuli. Salmons and Vrbova[9] first showed that continuous low-frequency electrical stimulation transforms fast-twitch fatigable muscle into the slow-twitch fatigue-resistant type. Such electrical stimulation has been applied to the gracilis sling operation in an attempt to achieve the fatigue resistance appropriate for sphincter function, with encouraging early clinical results[10,11]. There is, however, little evidence to demonstrate that electrical stimulation can transform fast-twitch human muscle. Similarly, the effects of muscle transformation and altered configuration, essential for neoanal sphincter construction, are unknown. The aim of this study was to compare the physiological and histochemical properties of the human gracilis muscle before and after construction of an electrically stimulated neoanal sphincter.

Patients and methods

Patients

Nineteen patients (14 female, five male; median age 48 (range 16–76) years) underwent gracilis neosphincter construction between December 1989 and June 1991, and have been followed for a median of 20 (range 8–26) months. Eleven patients (group 1) had faecal incontinence for a variety of reasons and eight (group 2) underwent neosphincter formation as part of a reconstructive procedure following sphincter excision or because of a congenital absence of sphincter muscle (*Table 1*). Details of the surgical procedures have been described previously[10]. All patients in the study underwent a preliminary vascular delay procedure a median of 5 (range 1–24) weeks before transposition to enhance the viability of the gracilis muscle during transposition and electrical stimulation[12].

Methods

The transposed gracilis was stimulated electrically with a totally implantable stimulator (initially Itrel; Medtronic, Minneapolis, Minnesota, USA, recently NICE implant; Neuromed, Fort Lauderdale, Florida, USA), programmed transcutaneously using a portable programmer. Stimulation was started more than 6 days after operation (median 15·5 (range 7–50) days). The nerve to the gracilis neosphincter was stimulated at its supramaximal voltage (range 0·25–6·0 V) with a pulse width of 210 μs to ensure utilization of all available motor units. Two different patterns of low-frequency stimulation were employed. In seven patients the neosphincter was stimulated continuously at 2 Hz; in 12 stimulation was intermittent at between 10 and 25 Hz. The 'on' times (4–10 s) and 'off' times (1–10 s) were altered at approximately 2-weekly intervals, such that the proportion of time that the muscle was activated was progressively increased. Once satisfactory neosphincter function was demonstrated by dynamic proctography[13] the covering stoma was closed (range 9–26 weeks). After stoma closure the muscle was stimulated at its supramaximal voltage using a stimulus pulse width of 210 μs and frequency of 10 Hz continuously in all cases.

Physiological measurements

Preoperative. Preoperative anal canal pressures were measured with a water-filled microballoon 6 mm in diameter connected to a pressure transducer, amplifier and chart recorder. The microballoon was inserted into the anal canal and the pressure recorded at 1-cm stations from 5 to 0 cm from the anal verge, at rest and during a maximum voluntary squeeze. The maximum basal pressure and

Table 1 *Indications for neosphincter surgery*

	No. of patients
Faecal incontinence (group 1)	
Trauma	
Obstetric	2
Surgical	2
Road traffic accident	1
Previous coloanal anastomosis	1
Rectal prolapse	2
Idiopathic (neurogenic)	3
Sphincter reconstruction (group 2)	
Congenital anorectal anomaly	3
After abdominoperineal resection	5

Winner of the Moynihan Prize at the meeting of the Association of Surgeons of Great Britain and Ireland in Jersey, UK, April 1992

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maximum achieved pressure were recorded. The maximum squeeze pressure was the difference between these two values.

Postoperative. Physiological assessment of the gracilis neosphincter muscle was undertaken in all patients before, and at regular intervals during, electrical stimulation by placing the microballoon in the (neo)anal canal at the site of maximum contraction. The following measurements were made:

1. *Pressure–frequency relationship.* Each neosphincter was stimulated at the supramaximal voltage and pulse width of 210 μs over a range of frequencies (2, 5, 10, 15, 20, 25 and 30 Hz). The pressure increment above the baseline at each frequency was recorded. The pressure generated was plotted against frequency of stimulation; this describes a sigmoid curve. To facilitate comparison between traces at different times, the frequency that generated 50 per cent of the maximum (fusion frequency) pressure was determined. This is termed the FF_{50}.
2. *Single twitch analysis.* The neosphincter was programmed to contract at 2 Hz continuously and the pressure was recorded. The time from the onset to the peak of each contraction (time to peak pressure) was recorded.
3. *Basal neosphincter pressure.* This was the pressure recorded at the site of the neosphincter when the stimulator was off.
4. *Maximum achieved neosphincter pressure.* This was the pressure recorded when the muscle was activated at tetany and supramaximal (or maximum tolerated) voltage.
5. *Maximum neosphincter squeeze pressure.* This was the difference between the basal neosphincter pressure and the maximum achieved pressure.
6. *Functioning neosphincter pressure.* This was the pressure generated at the site of the neosphincter after it had been activated continuously at 10 Hz. This was considered to be the patient's new functioning basal pressure or the 'sustainable' neosphincter pressure.

The functioning neosphincter pressure could be measured only in the 'relatively fatigued' state. It could not be determined during the electrical conditioning period or when the neosphincter was defunctioned by a temporary stoma. The neosphincter basal, maximum achieved and maximum squeeze pressures were measured after a rest period of 60 min.

Histochemical measurements

Biopsies were taken from the gracilis muscle at the various operative stages. Samples were removed at the first two operations when the whole muscle was exposed. Poststimulation biopsies were taken at the time of stoma closure under direct vision through a small incision placed about 5 cm from the anal canal. All biopsies were from the superficial aspect of the middle two quarters of the gracilis. In two patients a further biopsy was obtained after more than 16 months of low-frequency electrical stimulation during unrelated surgical procedures. Biopsies were orientated and snap-frozen in isopentane–liquid nitrogen. Sections 7 μm thick were cut and stained with myosin adenosine 5′-triphosphatase (ATPase) at various pH using a standard technique[14]. Under acid preincubation conditions, type 1 fibres stain darkly and type 2 fibres lightly; under alkaline conditions the reverse occurs. Type 2 fibres were not subdivided in this study.

The proportion of type 1 and 2 fibres was determined by counting at least 200 randomly selected fibres in each biopsy (a small number of biopsies contained fewer than 200 fibres, in which case all were counted). Fibre size was assessed by measuring the lesser diameter of 100 randomly selected fibres (of type 1 or 2) in each biopsy. To ensure a random selection of fibres, all those in a given microscope field were counted or measured. Fibres partly in one field and partly in another were not included. The slide was then moved 'blindly' to another part of the biopsy and all fibres in that field counted or measured. This process was continued until the required number of fibres had been assessed. To facilitate measurement the microscope was linked to a computerized analysis system (Magiscan; Joyce-Loebl, Gateshead, UK).

Statistical analysis and presentation of results

All results were expressed as median (95 per cent confidence interval). Comparisons between two groups were made using the Mann–Whitney *U* test for unpaired data or the Wilcoxon signed rank test for paired data. Comparisons involving more than two groups were made after preliminary analysis using the Kruskal–Wallis test for unrelated groups or the Friedman test for repeated observations on the same group of patients.

Results of measurements made on repeated occasions after neosphincter construction are expressed in various time epochs. Each patient is represented only once for a particular measurement in each epoch or not at all if no measurement was made during that period.

Results

Pressure–frequency relationship

The FF_{50} decreased significantly ($P < 0{\cdot}01$) after 31–90 days of low-frequency stimulation and remained decreased throughout the follow-up period (*Figure 1*).

In seven patients electrical stimulation was temporarily stopped for at least 4 weeks because of electrode plate displacement or perineal sepsis. The results of the FF_{50} before stopping electrical stimulation and after recommencement are shown in *Figure 2*. Between the initial assessment before starting stimulation and the last assessment before stopping stimulation the FF_{50} decreased in accordance with the overall results ($P = 0{\cdot}018$). At the first assessment after recommencement of stimulation the FF_{50} had reverted towards the original prestimulation value ($P = 0{\cdot}018$). Continued low-frequency electrical stimulation was associated with a further significant decrease in FF_{50} ($P = 0{\cdot}043$).

Stimulation of the gracilis neosphincter muscle at both 2 Hz continuously ($P < 0{\cdot}05$) and at 10–25 Hz intermittently ($P = 0{\cdot}004$) produced a significant decrease in FF_{50} (*Table 2*). There was no difference in the efficacy of the changes between the two frequency regimens.

Single twitches

The times to peak pressure of individual muscle twitches at various times after starting low-frequency electrical stimulation are shown in *Figure 3*. The time to peak pressure increased

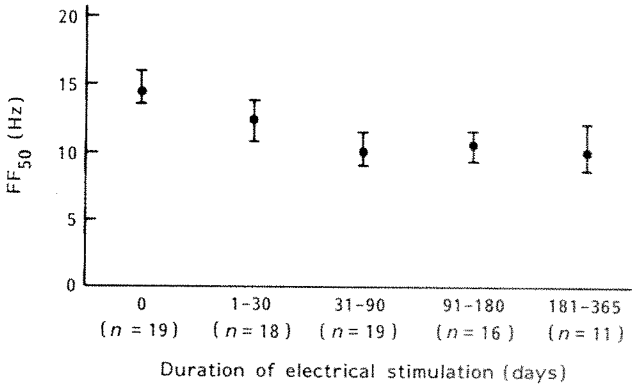

Figure 1 *Change in half-maximal fusion frequency (FF_{50}) with time. Values are median (95 per cent confidence interval).* P = *0·002 (Friedman two-way ANOVA)*

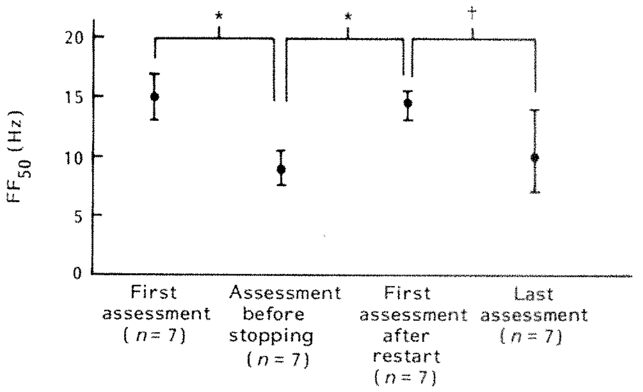

Figure 2 *Effect of temporary cessation of electrical stimulation on half-maximal fusion frequency (FF_{50}). Values are median (95 per cent confidence interval).* P = *0·0031 (Friedman two-way ANOVA);* *P = *0·018;* †P = *0·043 (Wilcoxon signed rank test)*

Table 2 *Effect of different stimulation regimens on half-maximal fusion frequency*

	Continuous stimulation at 2 Hz ($n = 7$)	Intermittent stimulation at 10–25 Hz ($n = 12$)
Prestimulation	15·0 (12·5–17·0)	14·5 (13·5–16·5)
After 30 days* of stimulation	11·0 (8·0–13·5)‡	11·0 (8·8–13·0)†

Values are median (95 per cent confidence interval) expressed in Hz. *Or assessment on closest day to day 30. †$P = 0{\cdot}004$; ‡$P < 0{\cdot}05$ (prestimulation *versus* 30 days, Wilcoxon signed rank test)

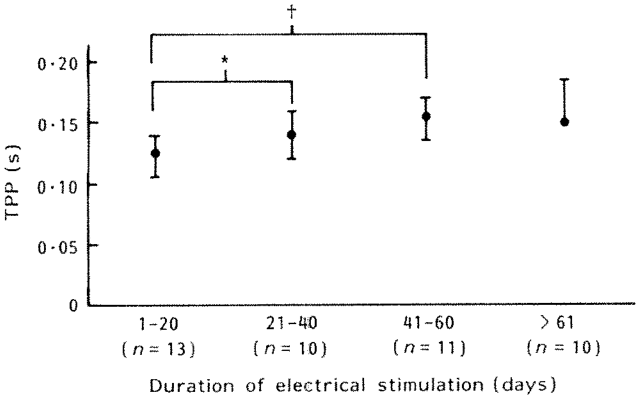

Figure 3 *Change in time to peak pressure (TPP) with time. Values are median (95 per cent confidence interval).* P = *0·0014 (Friedman two-way ANOVA);* *P = *0·025;* †P = *0·006 (Wilcoxon signed rank test)*

Table 3 *Anal canal pressures before and after operation*

	Group 1 median (95% confidence interval) pressure (cmH$_2$O) ($n = 11$)	Group 2 median (range) pressure (cmH$_2$O) ($n = 8$)
Preoperative maximum basal pressure	42·8 (32·5–55·5)	15·0 (8·0–22·5)
Basal neosphincter pressure	37·8 (32·5–47·0)	30·2 (22·0–35·0)
Functioning neosphincter pressure	63·0 (51·0–77·5)	47·8 (30·0–68·5)
Preoperative maximum squeeze pressure	13·0 (7·5–19·5)	8·5 (1·0–17·0)
Maximum neosphincter squeeze pressure	57·5 (45·0–106·5)	57·2 (38·5–87·5)

Maximum basal *versus* basal neosphincter pressure: group 1, *P* not significant; group 2, $P < 0{\cdot}05$. Functioning neosphincter *versus* maximum basal pressure: groups 1 and 2, $P < 0{\cdot}05$. Functioning neosphincter *versus* basal neosphincter pressure: groups 1 and 2, $P < 0{\cdot}05$. Maximum neosphincter squeeze *versus* maximum squeeze pressure: group 1, $P = 0{\cdot}003$; group 2, $P < 0{\cdot}01$ (Wilcoxon signed rank test)

significantly after 21–40 days ($P = 0{\cdot}025$) and further after 41–60 days ($P = 0{\cdot}006$) of low-frequency stimulation. It then remained increased throughout the follow-up period.

Preoperative and postoperative anal canal pressure (Table 3)

The postoperative basal neosphincter pressure did not change significantly during the follow-up period. For patients in group 1, the basal neosphincter pressure (taken as the mean of the last three assessments) was not significantly different from the preoperative maximum basal pressure ($P = 0{\cdot}037$). However, the eventual functioning neosphincter pressure was significantly greater than both the preoperative maximum basal ($P < 0{\cdot}05$) and postoperative neosphincter basal ($P < 0{\cdot}05$) pressures.

For patients in group 2, the basal neosphincter pressure was significantly greater than the preoperative maximum basal pressure ($P < 0{\cdot}05$) and the eventual functioning pressure was greater than both the neosphincter basal ($P < 0{\cdot}05$) and maximum basal ($P < 0{\cdot}05$) pressures.

The maximum neosphincter squeeze pressure (*Figure 4*) decreased significantly over the first 180 days of electrical stimulation ($P = 0{\cdot}004$), although then appeared to recover partially. The value at 181–365 days was significantly greater than at 91–180 days ($P = 0{\cdot}016$), but was still lower than the 0–30-day value ($P = 0{\cdot}008$). The maximum neosphincter squeeze pressure, arbitrarily taken as the mean of the last three measurements, was significantly greater than the preoperative maximum squeeze pressure for patients in groups 1 ($P = 0{\cdot}003$) and 2 ($P < 0{\cdot}01$).

Histochemical results (Table 4)

Of the 49 biopsies taken, 20 were found to be inadequate for quantitative analysis because the sample contained no muscle (or inadequate muscle) or because of freeze artefacts. The proportion of inadequate biopsies between the three operative stages was not significantly different.

In the biopsies taken before vascular delay, there was no difference in the proportion of type 1 fibres between male and female patients, and no correlation with age. Fibre diameters were significantly greater in male compared with female patients ($P < 0{\cdot}05$), although there was no association between age and

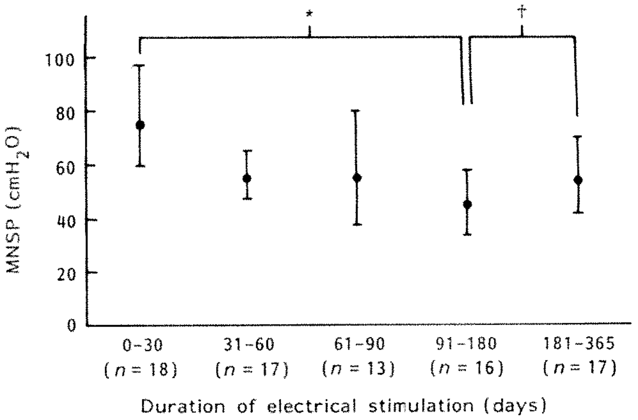

Figure 4 *Change in maximum neosphincter squeeze pressure (MNSP) with time. Values are median (95 per cent confidence interval).* P = *0·0063 (Friedman two-way ANOVA);* *P = *0·0043;* †P = *0·016 (Wilcoxon signed rank test)*

Table 4 *Histochemical results: percentage and diameter of type 1 and type 2 fibres*

	Stage 1 (before vascular delay; $n = 13$)	Stage 2 (after vascular delay, before stimulation; $n = 7$)	Stage 3 (after stimulation; $n = 7$)*
Percentage of type 1 fibres	34·0 (31·5–36·0)	30·0 (23·0–36·5)	67·2 (45·0–87·0)
Diameter of type 1 fibres (μm)	36·8 (32·2–45·9)	42·4 (33·5–45·9)	30·2 (25·5–32·8)
Diameter of type 2 fibres (μm)	32·8 (25·5–39·9)	35·5 (25·5–47·0)	27·8 (15·8–38·9)

Values are median (95 per cent confidence interval). *At time of stoma closure (median duration 80 (range 49–137) days after transposition). No significant differences were found between stages 1 and 2, or between any stage for type 2 diameter. Percentage of type 1 fibres: stage 1 *versus* stage 3: $P = 0{\cdot}004$; stage 2 *versus* stage 3: $P = 0{\cdot}002$. Diameter of type 1 fibres: stage 1 *versus* stage 3: $P = 0{\cdot}02$; stage 2 *versus* stage 3: $P < 0{\cdot}02$ (Mann–Whitney *U* test) fibre diameter in this group. In all biopsies from female (but not male) patients, type 1 fibres were larger than those of type 2 ($P < 0.01$). There was no significant difference in the percentage of type 1 fibres nor in their diameter after the preliminary vascular delay procedure.

Gracilis muscle transposition and low-frequency electrical stimulation (mean duration 80 (range 49–137) days) was associated with a significant increase in the proportion of type 1 fibres (*Table 4*). The diameter of such fibres after electrical stimulation was significantly less than that before transposition and stimulation.

Two late biopsies taken 16 and 21 months after starting low-frequency electrical stimulation showed an increase in the proportion of type 1 fibres compared with earlier samples from the same patients (61 and 98 per cent type 1 fibres for one patient, 45 and 81 per cent for the second). The fibre diameters did not appear to change markedly between the early and late poststimulation biopsies.

Discussion

Electrical stimulation of the gracilis neosphincter may provide additional benefit compared with the conventional gracilis sling operation for two reasons. First, the stimulator gives the neosphincter properties of active contraction and passive relaxation that may be voluntarily controlled by the patient using a small magnet placed over the device. Second, electrical stimulation may convert fast-twitch muscle to that of slow-twitch type, giving the muscle the additional useful property of fatigue resistance. The results of the present study confirm the ability of electrical stimulation to produce this transformation in human muscle.

There was a significant decrease in FF_{50} after 21 or more days of low-frequency electrical stimulation. This means that twitch summation and tetanic fusion are occurring at a lower frequency. Similarly, the time to peak pressure increased after stimulation. These changes are indicative of transformation from fast to slow muscle[15].

In isolation, these physiological changes cannot be considered proof of muscle fibre type conversion. Other changes such as muscular or perimuscular fibrosis or an adaptation to a change in muscle length[16] after transposition could produce similar results. However, the histochemical studies indicate that transposition and electrical stimulation results in a significant increase in the proportion of type 1 fatigue-resistant fibres. The myosin ATPase technique is the standard method to assess muscle fibre type[14]. It is interesting that the two late biopsies showed a further increase in the proportion of type 1 fibres, suggesting that in these patients transformation was incomplete at the time of stoma closure and continued afterwards. However, the physiological changes were apparent after only 21 days of low-frequency stimulation.

The reversibility of changes in FF_{50} (*Figure 2*) is additional evidence that the physiological effects result from muscle fibre type conversion. If the changes were caused by fibrosis or a change in muscle length, they would be unlikely to be reversible. Furthermore, in each of the seven patients in whom electrical stimulation was temporarily stopped, the degree of continence deteriorated during the period of no stimulation compared with that of continuous stimulation. These observations emphasize the need for continued stimulation.

Both patterns of low-frequency electrical stimulation used produced changes consistent with conversion from fast- to slow-twitch muscle. This supports the generally held view that it is the increase in overall (or aggregate) neuronal activity that is responsible for changes in the characteristics of skeletal muscle[7,17]. No difference in the efficacy of muscle transformation was noted between the two patterns, although further studies are required to compare different stimulation regimens.

The maximum pressure that the neosphincter could generate decreased significantly over the first 6 months of electrical stimulation, then underwent a partial but significant recovery (*Figure 4*). The diameter of type 1 fibres decreased significantly following transposition and stimulation. The diameter of type 2 fibres also decreased although the change was not statistically significant, perhaps because there were relatively few type 2 fibres available for measurement in many of the poststimulation samples.

A reduction in fibre diameter may be an inevitable consequence of electrical stimulation. The mean fibre diameter of the rabbit tibialis anterior muscle decreased by 25 per cent after 4–6 weeks of low-frequency stimulation *in situ*[7]. It has been suggested that decrease in fibre size may be a factor in enhancing fatigue resistance by reducing the diffusion distance between capillaries and the centre of fibres[18]. A much more profound reduction in muscle strength has been observed with latissimus dorsi cardiomyoplasty[19], in which the latissimus dorsi muscle is transposed into the thorax, wrapped around the heart and stimulated electrically to augment or replace ventricular function. Salmons and Jarvis[20] reported an 80 per cent reduction in acute power output of the latissimus dorsi muscle following this procedure. This may be because, in cardiomyoplasty, the latissimus dorsi is not resutured to bone after transposition. In the gracilis neosphincter procedure the muscle is fixed to the ischial tuberosity. This may maintain sufficient stretch to reduce the degree of muscle atrophy.

The reduction with time in pressure-generating capacity of the gracilis neosphincter may eventually compromise function; future research should be directed at limiting this problem. There is recent evidence that patterns incorporating a 'background' of low-frequency stimulation plus intermittent very short bursts of high-frequency stimulation (100 Hz) may result in transformation into a slow-twitch fatigue-resistant muscle but with preservation of muscle mass[19,21]. Alternatively, optimizing the degree of muscle stretch during neosphincter construction may minimize muscle atrophy. Goldspink *et al.*[22] demonstrated that electrical stimulation of an understretched muscle results in atrophy, whereas stimulation of a stretched muscle may increase its mass.

The observed significant recovery in the maximum neosphincter squeeze pressure in the present study between 6 and 12 months is intriguing and may represent continued adaptation by the gracilis muscle to its new location or function. Further studies are needed to confirm this partial recovery and to investigate its underlying cause.

The basal neosphincter pressure was not found to be significantly different from the preoperative maximum basal pressure for patients with faecal incontinence. This may help to explain the generally poor results of the conventional gracilis sling operation performed without stimulation[6]. In contrast, the sustainable pressure generated by the neosphincter was significantly greater than both the maximum basal and basal neosphincter pressures, confirming the utility of prolonged stimulation.

In summary, this study has demonstrated that the human gracilis muscle is capable of physiological and histochemical adaptation to long-term neosphincter function. The reversibility of the physiological changes emphasizes the importance of continued electrical stimulation.

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Paper accepted 29 January 1993

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, October, 1347–1348

A selection from the September issue of the American journal.

Reduction of systemic drug exposure after hepatic arterial infusion of doxorubicin with complete hepatic venous isolation and extracorporeal chemofiltration

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Background. *Hepatic arterial infusion of doxorubicin has produced tumor response in hepatic malignancies; however, the limited success of these treatments is related in part to dose-limiting systemic toxicities. The purpose of this study was to determine whether a novel venous isolation–chemofiltration system could limit systemic exposure to doxorubicin after hepatic arterial infusion.*
Methods. *Doxorubicin (1 or 3 mg/kg) was infused in the hepatic arteries of domestic pigs after complete hepatic venous isolation was achieved with a dual-balloon vena cava catheter. The hepatic vein effluent was pumped through an extracorporeal carbon chemofiltration circuit. Doxorubicin levels were measured in prefilter (hepatic vein), postfilter, and systemic serum at intervals up to 1 hour after drug infusion.*
Results. *Complete hepatic venous isolation with extracorporeal chemofiltration significantly reduced (>90%) the postfilter and systemic levels of doxorubicin compared with prefilter levels ($p < 0.01$). At the time animals were killed 7 days after infusion of doxorubicin (3 mg/kg), tissue levels of doxorubicin in the liver showed a 16-fold increase compared with levels in the heart ($p < 0.01$).*
Conclusions. *For chemotherapeutic drugs like doxorubicin with a low first-pass extraction by the liver, the novel system described herein achieved significant reduction in systemic drug exposure. This system will allow dose intensification of doxorubicin administered by hepatic arterial infusion to treat hepatic malignancies. (*SURGERY *1993;114:579-85.)*

Interleukin-6 mediates host defense responses induced by abdominal surgery

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Background. *Cytokines have been implicated as pivotal mediators of the host defense reaction. In patients undergoing surgery we investigated the relationship between such mediators and postoperative host defense responses.*
Methods. *Tumor necrosis factor (TNF) was determined with an immunoradiometric assay, interleukin (IL)-6 by a B9-cell bioassay, and endotoxin by a chromogenic* Limulus *lysate assay. C-reactive protein, α_1-antitrypsin, and α_2-macroglobulin were quantified by nephelometric assay.*
Results. *In 19 consecutive patients undergoing pancreaticoduodenectomy, a large increase in portal, and a significantly lower increase in peripheral, IL-6 levels was observed. No significant increase in TNF levels was noted. Fever developed in 16 patients within 24 hours (84%). The highest peripheral IL-6 levels correlated logarithmically ($R = 0.59$; $p = 0.0039$) with the peak body temperatures. C-reactive protein levels correlated with IL-6 levels ($R = 0.49$; $p = 0.020$). Increased IL-6 levels were observed in all nine patients undergoing either hemihepatectomy, breast reduction, or extensive breast reconstruction; however, only patients undergoing hemihepatectomy had endotoxemia.*
Conclusions. *We conclude that abdominal surgery causes acute release of IL-6, but not TNF, in the portal circulation. IL-6 seems to be a major endogenous mediator of fever and the acute-phase response. The presence of endotoxin might be synergistic but is not obligatory for the host defense response after surgical trauma. (*SURGERY *1993;114:564-70.)*

The effect of acute nonbacterial dependent peritonitis on lung and liver oxidant stress and antioxidant activity

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Background. *The role of oxidant release and tissue antioxidant defenses on inflammation-induced organ injury is not clearly defined.*
Methods. *We determined the effect of acute zymosan peritonitis in rats on lung and liver tissue oxidant stress and antioxidant defenses during a 5-day period. Oxidant activity was measured as tissue malondialdehyde and oxidized glutathione (GSSG). Antioxidant activity was measured as tissue-reduced glutathione (GSH) and catalase activity. Rats were maintained hydrated with subcutaneous crystalloid. Animals were killed at 4, 12, and 24 hours and 5 days.*
Results. *Acute peritonitis was evident at 12 and 24 hours but was resolving at 5 days. Peritoneal fluid cultures were negative after 24 hours. A 50% mortality rate was noted between 20 and 30 hours, with no deaths after 30 hours. We noted a significant increase in lung GSSG and malondialdehyde at 4 hours that persisted for the 5 days, as did histologic evidence of a progressing severe lung inflammation. No increased conversion of lung xanthine dehydrogenase to xanthine oxidase was noted. Lung GSH and catalase activity were maintained at*

control despite negligible food intake. In contrast, liver GSSG was increased significantly only at the 4-hour period, corresponding with a transient conversion of xanthine dehydrogenase to xanthine oxidase from 10% to 31%. Tissue malondialdehyde did not increase despite the initial oxidant stress. However, tissue GSH and catalase values decreased by more than 50% after 24 hours and remained decreased at 5 days.

Conclusions. *We conclude that early lung and liver oxidant stress is initiated by acute peritonitis. Lung oxidant changes persist and lung dysfunction progresses, even though antioxidant activity is maintained and acute peritonitis is resolving. Liver lipid peroxidation did not develop despite oxidant release, probably because of a large antioxidant reserve. However, a severe and sustained decrease in liver antioxidants results, increasing the potential damage from a subsequent oxidant insult. (SURGERY 1993;114:571-8.)*

The effect of erythromycin on motility of the duodenum, sphincter of Oddi, and gallbladder in the prairie dog

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Background. *Interdigestive motility of the stomach, duodenum, sphincter of Oddi, and gallbladder is mediated through the migrating myoelectric complex and the action of motilin. Erythromycin, a motilin agonist, has recently been studied as a gastrointestinal and biliary prokinetic agent. We hypothesized that erythromycin would increase interdigestive duodenal and sphincter of Oddi motility in a dose-dependent manner.*

Methods. *In 10 anesthetized prairie dogs we determined the motility responses of the duodenum, sphincter of Oddi, and gallbladder to erythromycin infusion during a three-log dosing regimen and correlated activity with serum concentrations of the drug.*

Results. *Erythromycin administered at 0.01 and 0.1 mg/kg had no effect on duodenal or sphincter motility. At 1.0 and 10 mg/kg, duodenal motility index increased by 451% ± 114% and 1070% ± 480%, respectively, when compared with baseline values ($p < 0.05$). Sphincter of Oddi motility index increased by 122% ± 38% and 323% ± 99%, respectively, at these same doses of erythromycin ($p < 0.05$). Gallbladder pressure did not change significantly during erythromycin infusion. Erythromycin serum concentration at 1.0 mg/kg was 1.0 ± 0.7 μg/ml.*

Conclusions. *These data suggest that erythromycin stimulates interdigestive motility of the duodenum and sphincter of Oddi in a dose-dependent manner at otherwise subtherapeutic concentrations of the drug. (SURGERY 1993;114:543-8.)*

Safe intraabdominal pressure of carbon dioxide pneumoperitoneum during laparoscopic surgery

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Background. *The deliberate induction of carbon dioxide pneumoperitoneum during laparoscopic surgery could be a possible source of cardiovascular collapse. The effects of elevated intraabdominal pressure (IAP) on systemic hemodynamics and splanchnic blood flow created by insufflation of carbon dioxide were examined in anesthetized dogs.*

Methods. *Stepwise increases in IAP of 8 ($n = 7$), 12 ($n = 7$), and 16 ($n = 7$) mm Hg were applied to determine the threshold pressure that had minimum influence on these hemodynamics. Hemodynamic parameters were measured at baseline and 1, 2, and 3 hours after the start of insufflation.*

Results. *At an IAP of 16 mm Hg, cardiac output was decreased significantly by 1 hour after the start of insufflation and became progressively lower during the procedure. Systemic vascular resistance was elevated significantly in parallel with the change in cardiac output. Although hepatic arterial blood flow was not decreased significantly, portal venous and superior mesenteric arterial blood flows were diminished significantly at 16 mm Hg, resulting in a decrease in total hepatic blood flow. No significant changes were observed in these parameters at 8 or 12 mm Hg.*

Conclusions. *Based on these results, an IAP from 8 to 12 mm Hg is recommended for laparoscopic surgery, to avoid complications caused by hemodynamic derangements. (SURGERY 1993;114:549-54.)*

Growth-related gene expression in early cholestatic liver injury

Thomas F. Tracy, Jr., MD, Mary E. Goerke, BA, Patrick V. Bailey, MD, Cirilo Sotelo-Avila, MD, *and* **Thomas R. Weber, MD,** *St. Louis, Mo.*

Background. *Extrahepatic biliary obstruction initiates cholestasis, bile duct proliferation, periportal fibrosis, and, eventually, lethal biliary cirrhosis. Little is known about the genetic regulation of the cellular proliferation and differentiation that begins with the onset of bile duct obstruction. To focus this and future gene expression studies, we sought to determine the time frame for growth-related gene expression and questioned whether the in vivo expression of the protooncogenes H-ras and c-myc was altered after bile duct obstruction.*

Methods. *Female Fisher rats underwent ligation and division of the common bile duct or sham laparotomy.*

Results. *After obstruction, serum bilirubin and γ-glutamyl transpeptidase rose to 24% and 30%, respectively, of maximum levels by 10 days after ligation. Morphologic evidence of proliferation of bile duct epithelial cells was first evident after 3 days. After hybridization to c-DNA probes, densitometry for H-ras and β-actin revealed an immediate and parallel increase in steady-state levels of expression after 24 hours of cholestasis. Levels of c-myc messenger RNA were elevated during the first 3 days of cholestasis; however, at 7 and 10 days c-myc expression was depressed 16% and 60%, respectively.*

Conclusions. *These profiles of expression show an oncogene response induced by early cholestasis. These data showed that elevations in H-ras and c-myc steady-state expression accompany the proliferative response of bile duct epithelial cells. Decreased levels of c-myc after initial elevation infer that ductal proliferation may continue independently of its steady-state expression, a response usually seen in vitro rather than in vivo proliferation. (SURGERY 1993;114:532-7.)*

Correspondence

Herniation at the site of cannula insertion after laparoscopic cholecystectomy

Letter 1

Sir

We read with interest the recent Case Report by Messrs McMillan and Watt (*Br J Surg* 1993; **80**: 915). We have previously reported the complication of small bowel herniation through the umbilical wound from a 10-mm port, resulting in obstruction that required small bowel resection[1]. In this case the gallbladder had also been removed through the epigastric cannula, suggesting that a wound of 10 mm is sufficient for this problem to arise. We believe that the complication has not been encountered following gynaecological laparoscopy as nearly all procedures use 5- or 8-mm cannulas. We had attempted closure of the defect with a 2/0 polyglactin suture, and feel this illustrates the difficulties encountered in closure of the fascial layer through such a small incision. We have found the use of a J shaped needle facilitates closure of the wound. The report of small bowel obstruction secondary to suturing of the small bowel to the abdominal wall demonstrates the need for adequate exposure for the placement of sutures under direct vision[2]. Although the wounds are small and some believe closure to be unnecessary, further reports of this nature may help settle the debate of whether to close fascial defects after laparoscopic surgery.

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Letter 2

Sir

I read with interest the Case Report by Messrs McMillan and Watt (*Br J Surg* 1993; **80**: 915) describing herniation at the site of cannula insertion after laparoscopic cholecystectomy. The authors state that theirs is the first report of intestinal obstruction secondary to bowel entrapment at the site of an incision used for a 10-mm laparoscopic cholecystectomy port. In fact a very similar case was reported by Boyce and colleagues[2] in July 1992. They described a patient developing small bowel obstruction in the immediate postoperative period caused by entrapment of a loop of small bowel at the fascial defect occurring at the site of insertion of the umbilical cannula. A further case of the same complication was described in the series of Martin and colleagues[2] in August 1992.

In a personal series of 133 laparoscopic cholecystectomies (54 as cameraman, 25 as operator under supervision, 54 as principal operator) I encountered the same complication in patient 6 in this group. She presented 6 weeks after operation with a lump at the site used for the epigastric cannula. At operation a small hernia containing small bowel was found and repaired. It is of interest that in this patient the fascia had not been sutured. Having subsequently read reports of this complication, the fascial defect at the site of the epigastric and umbilical cannula sites has been repaired using no. 1 polydioxanone on a J needle in all patients. There have been no further hernias. Although this is a rare complication, it seems reasonable practice to repair a defect of $\geqslant 10$ mm in size in the anterior abdominal wall. Anxiety regarding the possibility of picking up a loop of small bowel during closure of the fascial defect can be minimized by leaving the camera in place to inspect the underside of the epigastric wound after repair.

Finally, all four cases describe hernias at the site of 10-mm cannulas. Herniation at the smaller 5-mm cannula sites is less likely because of the smaller defect and, possibly, because these cannulas are inserted more obliquely so that the skin puncture site may be 2–3 mm from the point of entry into the peritoneal cavity.

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Laparoscopic abdominoperineal resection of the rectum

Sir

I read with interest the comments of Dr Rehman (*Br J Surg* 1993; **80**: 1080) regarding my article (*Br J Surg* 1992; **79**: 1207–8). I fully agree that for abdominoperineal resection for carcinoma the inferior mesenteric artery must be ligated high and early, and would point out that the first case that I reported was performed for benign disease. While I agree that the operation can be done with four ports, I do not think that one should 'gild the lily' by struggling. Although I would normally now use four ports for all colonic and rectal procedures, if I have any problems I put a fifth one in. I was intrigued by Dr Rehman's use of a plastic rod to manipulate the rectum – I have merely used a rigid sigmoidoscope to achieve this end. However, I do feel that the technique to create the colostomy reported by him runs the risk of contaminating the abdominal cavity. One of the problems with laparoscopic bowel surgery is ensuring that the abdomen remains clean. My technique of stapling the bowel closed prevents any chance of faecal spillage, which a purse string does not. As far as time taken to perform the operation is concerned, certainly with increasing experience it gets faster. I thank Dr Rehman for his useful technical tips; we must all continue to trade 'secrets' to ensure skills in this area are improved.

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Conventional *versus* laparoscopic surgery for acute appendicitis

Sir

The recent paper by Mr Tate and colleagues (*Br J Surg* 1993; **80**: 761–4) raises a number of interesting questions about the role of laparoscopic appendicectomy. Our experience is very similar to that described (*Table 1*). Of the first 48 attempted laparoscopic appendicectomies, three were converted to open procedures, all within the first month of using this technique. In each case the appendix was gangrenous or perforated. We are now happy to deal with an appendix that is inflamed right down to the caecum, using intracorporeal suturing of the base where necessary. Surgeons genuinely experienced in laparoscopic cholecystectomy, especially in patients with acute cholecystitis, should have a rapid 'learning curve' for laparoscopic appendicectomy. Our mean operating time for completed cases was 52 (range 20–105) min; this includes time from induction of anaesthesia to dressing the incisions. Compared with a group of patients matched for age, sex and severity of appendicitis who underwent conventional

Table 1 *Laparoscopic* versus *conventional appendicectomy*

	Laparoscopic ($n = 45$)	Conventional ($n = 45$)
Doses of intramuscular analgesia*	3 (0–9)	3 (0–8)
Hospital stay (days)*	4	4
Wound infection	0	1
Pelvic or abdominal abscess	0	0

*Values are median (range)

appendicectomy, the laparoscopic approach conferred no advantage in terms of postoperative analgesia requirement or length of hospital stay. There were no wound infections in the laparoscopic group, although there was one port haematoma. None of the patients developed an intra-abdominal abscess.

The operation does not therefore appear to carry the advantages that have been well documented for the laparoscopic approach to cholecystectomy or Nissen fundoplication. We doubt the value of randomized trials comparing laparoscopic with conventional appendicectomy.

Attention in further studies need to be directed towards return to normal activities in the period after discharge and whether patients find three laparoscopic scars more acceptable than the usual wound in the right iliac fossa.

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Contemporary management of the appendiceal mass

Sir

I take issue with the comments of Messrs Sargeant and Mason, and Mr Ridings concerning the management of appendiceal mass (*Br J Surg* 1993; **80**: 810).

Sargeant and Mason regard as 'speculative' the fact that 80 per cent of patients recovering from an appendiceal mass will not require subsequent appendicectomy. This figure is, however, based on well documented studies[1]: of a total of 207 patients followed for between 6 months and 22 years without interval appendicectomy, only 22 (10·6 per cent; range 0–20 per cent) suffered recurrent appendicitis. I agree that those travelling to remote locations should be offered elective appendicectomy and have previously stated this advice[1]. Sargeant and Mason also claim that delay in diagnosis of caecal tumours will result if interval appendicectomy is omitted. This pitfall can be obviated if all patients with an appendiceal mass subsequently undergo barium studies or colonoscopy.

Mr Ridings' argument that percutaneous abscess drainage is not always available is correct, but most patients can be managed entirely conservatively, with neither percutaneous nor operative drainage but with successful outcome[2] within 10 days. His lucky experience with immediate appendicectomy in five cases contrasts with the warnings of others that immediate appendicectomy is fraught with complications and the danger of misdiagnosing the appendiceal pathology[1,2].

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Single-loop biliary and gastric bypass for irresectable pancreatic carcinoma

Sir

We read with interest the paper by Dr Watanapa and Professor Williamson (*Br J Surg* 1993; **80**: 237–9) about a biliary and gastric bypass with a single retrocolic Roux loop. We appreciate the need for a simple and effective palliative procedure in irresectable pancreatic cancer, but with our experience in 51 patients favour a single-loop biliary and gastric bypass even without enteroanastomosis.

This technique was introduced by Dr R. Hermann[1]. The first loop of the jejunum is used for an antecolic isoperistaltic side-to-side gastrojejunostomy to the gastric antrum (two-layer or stapled anastomosis 7·5 cm in length) and 10–15 cm distally for a biliary end-to-side anastomosis to the fundus of the gallbladder (one-layer or stapled anastomosis 5·0 cm in length). In the presence of gallstones, after previous cholecystectomy or in cases of cystic duct junction close to the tumour, anastomosis to the common hepatic duct is performed.

Since 1986 we have carried out this procedure on 28 female and 23 male patients with a median age of 67 (range 44–82) years. The median operating time was 2·0 (range 1·0–3·0) h, markedly shorter than in Watanapa's patients (4·0 (2·5–6·0) h), but we certainly agree that the operating time is influenced by the exploration of resectability. Minor postoperative complications occurred in ten patients and seven died within 30 days. Two patients suffered from cholangitis, a further two developed delayed gastric emptying despite a patent gastroenterostomy, and peptic ulcer complications required treatment with H_2-blockers in four patients. Serum bilirubin levels showed an adequate decrease in 48 patients. The median hospital stay after operation was 18 (range 9–40) days and median postoperative survival 5 (range 0–13) months.

Concerning the discussion about cholecystojejunostomy or choledochojejunostomy[2,3], we prefer primarily the use of the gallbladder as the technically simplest procedure in these patients with limited life expectancy. Our functional results in 43 patients are as good as for hepaticojejunostomy, which was necessary in eight patients.

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1. Hermann RE. *Manual of Surgery of the Gallbladder, Bile Ducts and Exocrine Pancreas*. New York: Springer, 1979: 298.
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Authors' reply

Sir

We thank Dr Lindemann and his colleagues for their letter. The point at issue is whether to use the gallbladder or common hepatic duct for anastomosis to the jejunum during bypass surgery for irresectable cancer of the pancreatic head. If the bile duct is chosen it may be technically simpler to use a Roux loop rather than jejunum in continuity, even though this necessitates an additional anastomosis.

Our own preference for cholecystectomy and choledochojejunostomy is based on personal observation. A substantial experience of pancreatoduodenectomy for chronic pancreatitis has underlined the frequency with which the cystic duct joins the common hepatic duct low down, i.e. close to the duodenum. Often the ducts appear to join at a higher level, but this proves to be an adventitial fusion and not the true luminal junction. Thus, if the cystic duct is to be used as a conduit for biliary bypass we regard on-table cholecystography as essential. Dr Lindemann does not report the incidence of early recurrent jaundice in his large series of cholecystojejunostomies, but we have had to reoperate on three such patients. One case was particularly instructive.

A 68-year-old woman underwent laparotomy for an apparently favourable carcinoma of the pancreatic head, but resection was abandoned because the tumour was fixed posteriorly. At this stage the systolic blood pressure fell to 40 mmHg and remained unresponsive to pressor drugs (including intracardiac adrenaline). Myocardial infarction was suspected, and we were encouraged by the anaesthetist to terminate the operation as soon as possible. A rapid cholecystojejunostomy was therefore carried out instead of the standard Roux loop bypass to stomach and bile duct that was described in our paper. During abdominal closure the patient's blood pressure improved spontaneously and she made a completely uneventful recovery; she received subsequent radiotherapy. Some 4 months later the woman became jaundiced again. Imaging revealed an obstructed cystic duct but no evidence of distant disease. At a second laparotomy the tumour was still irresectable. The gallbladder was removed and a single Roux loop was brought up for separate bile duct and gastric anastomoses. She remained in good health for several months, dying quickly from carcinomatosis 13 months after the original operation. It is ironic that her length of survival was greater than that of any of the other 25 patients reported in our paper.

Our policy is therefore to try to separate patients with carcinoma of the head of pancreas into two groups at the time of admission. Those who are unsuitable for operation by reason of extreme age, intercurrent disease or advanced cancer are treated with an expandable metal biliary stent. The younger fitter patients without extensive metastases are submitted to operation after imaging studies that include endoscopic retrograde cholangiopancreatography, computed tomography and (usually) visceral angiography. Resectable tumours are excised, and the other patients receive single-loop biliary and gastric bypass. With this protocol there is little or no indication for cholecystojejunostomy: those with a very limited prognosis should already have been identified and treated by stenting.

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Endoscopic sympathectomy

Sir

Mr Hederman's timely Leading Article on thoracoscopic sympathectomy (*Br J Surg* 1993; **80**: 687–8) correctly stresses the superiority of this method over conventional cervical sympathectomy. In our experience of 95 sympathectomies in 49 patients, all those with hyperhidrosis were pleased with the initial results. However, we are concerned that, although perioperative and postoperative complications are uncommon, they may have disastrous consequences if their management is suboptimal.

Three of our patients developed appreciable and sustained hypoxia during the procedure, this phenomenon having also been noted by others[1]. In these cases it may be advisable to limit the procedure and carry out the second sympathectomy at a later date. We are currently studying the use of continuous high-frequency jet ventilation of both lungs in an attempt to reduce the incidence and degree of hypoxia. Pneumothorax requiring an underwater seal drain is a relatively frequent complication, occurring in 16 of our 49 patients, and may be serious *if not recognized early*. We recommend that all patients have chest radiography immediately after operation.

The risk of these complications should not be underestimated, especially when one considers that most procedures are performed on otherwise healthy young patients for cosmetic and social indications. Because of these potential problems, we believe that proficiency in laparoscopic surgery alone is not sufficient, and that surgeons and anaesthetists involved in these procedures should have had adequate training in thoracic surgery and anaesthesia.

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Prospective randomized study of one- or two-layer anastomosis following oesophageal resection and cervical oesophagogastrostomy

Sir

I was very interested in the paper by Dr Zieren and colleagues (*Br J Surg* 1993; **80**: 608–11) on cervical oesophagogastrostomy. Having had experience of this technique since I first performed it in 1960, I would like to make the following comments, which are somewhat at variance with those made by my colleagues.

First, anastomosis in the neck results (in my experience) in fewer leaks than that in the chest, probably because of the ease of anastomosis in the superficial layer in the neck. Second, leaks in the chest are in my experience almost always fatal, whereas those in the neck are not. Third, regarding the type of anastomosis, I favour that with interrupted vertical mattress sutures using 3/0 ivory Mersilene (Ethicon, Edinburgh, UK) with the sutures spaced at intervals of 3 mm and the knots tied on the lumen. This suture line is supported by a continuous catgut suture involving only the outer layers of the anastomosis[1]. This type of anastomosis is very different from the two-layer construction shown in *Figure 1a* of their paper and is somewhat similar to that illustrated in *Figure 1b*, except that the knots are tied on the lumen and not on the outside. The second layer in the type of anastomosis that I recommend is a continuous catgut layer involving only the outermost layers of the oesophagus. Finally, I think that stricture following anastomosis can be avoided by employing two features: the oesophagus should be sectioned obliquely to increase the length of the stoma and the opening in the stomach should be crescentic[2].

My own conclusion after 30 years of experience in this field is that total oesophageal replacement with cervical anastomosis is a safer and better procedure than the two-phase technique.

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1. McKeown KC. Total three stage oesophagectomy for cancer of the oesophagus. *Br J Surg* 1976; **63**: 259–62.
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Laparoscopic mobilization and exteriorization for minimally invasive small bowel resection

Sir

I read with interest the Surgical Workshop by Mr Attwood and colleagues (*Br J Surg* 1993; **80**: 225). Using this technique, I resected a leiomyoma of the small intestine that had caused recurrent episodes of heavy gastrointestinal bleeding before a diagnosis was made using an isotope scan. I agree with Mr Attwood and colleagues that, at least with the instruments currently available, extracorporeal resection and anastomosis is far superior to intracorporeal methods. Going a step further, I would propose this technique as the method of choice when dealing with large bowel obstruction.

The presence of distended large bowel makes intracorporeal handling, decompression, mobilization and resection very difficult. A 4–5-cm transverse incision is made at a point where a possible colostomy stoma may be sited. A segment of distended colon is delivered using atraumatic graspers, and through a purse-string suture the colon is decompressed using suction. This segment will then act as a plug to stop carbon dioxide leakage, while pneumoperitoneum is established using a cannula inserted through the same incision and accessory trocars are inserted. Mobilization of the colon is carried out to the required extent, and the mobilized segment is pulled out and resected. Thereafter the surgeon may choose to establish a colostomy or perform primary anastomosis extracorporeally.

This technique has many advantages that make it worth considering. Extracorporeal decompression allows better laparoscopic assessment and prevents intraperitoneal spillage of bowel contents. Pneumoperitoneum is established through a cannula placed next to the exteriorized segment after decompression, thus removing the risk of bowel injury. Traction on the exteriorized segment facilitates laparoscopic mobilization as it places peritoneal attachments and the mesocolon under tension. Finally, when this technique is used to establish a colostomy, second-stage surgery may be easier and can be performed sooner than after conventional procedures.

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'Car-crusher colon'

Sir
Mr Whiteley and colleagues (*Br J Surg* 1993; **80**: 640) state that 'degloving' of the colonic outer wall has not previously been reported. Not so, for two reports exist in which such circumferential split-thickness transection of the intestinal wall occurred in vehicular accidents and was reported as seromuscular rupture[1,2]. The injury results from shearing forces induced by rapid deceleration, whereby the seatbelt strikes the intestinal wall.

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1. Appleby JP, Nagy AG. Abdominal injury associated with the use of seatbelts. *Am J Surg* 1989; **157**: 457–8.
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Randomized trial comparing three forms of pelvic floor repair for neuropathic faecal incontinence

Sir
Professor Keighley's group reported (*Br J Surg* 1993; **80**: 794–8) an interesting trial that compared anterior sphincter plication alone, postanal repair and the two operations combined (total pelvic floor repair), and found that the combined operation is better.

Sultan *et al.*[1] demonstrated new sphincter defects in more than one-third of women following their first vaginal delivery. Furthermore, even when there is no clinical suspicion of sphincter injury, 36 per cent of patients with electrophysiologically confirmed pudendal neuropathy may have a sphincter defect demonstrated using anal endosonography[2].

Thus, in the absence of anal endosonography, there will be some women with a pure pudendal neuropathy and others with a combined sphincter injury and neuropathy despite the authors' attempts to exclude such patients. It is hardly surprising that these patients do better when their anterior sphincter injury is also attended to by anterior sphincter plication. Perhaps it is because of this that the trial found for total pelvic floor repair. What is not clear from the published data is whether, *given normal findings on anal endosonography*, anterior sphincter plication adds anything to postanal repair.

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1. Sultan AH, Kamm MA, Hudson CH, Bartram CI. Vaginal delivery causes anal sphincter disruption in 37% of patients (prospective ultrasound study): a major determinant for development of faecal incontinence. *Gastroenterology* 1992; **102**: A522 (Abstract).
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Authors' reply

Sir
In response to the letter by Messrs Loder and Phillips, we confirm that routine anal ultrasonography was not available when all patients were being admitted to the pelvic floor repair trial, hence the suggestion that some of them might have had a clinically undetected anterior external sphincter injury is a possibility. Nevertheless, 3-year experience with anal ultrasonography on these groups of patients subsequent to the trial has led us to conclude that our clinical impression of complete sphincter division is accurate. We do accept that partial weakness of the external sphincter may be undetected clinically. Since it has always been our policy to perform an overlapping sphincter repair if there is an actual break in the external sphincter, such patients would never have been admitted to the trial in any case. We acknowledge that some weakness of the external anal sphincter anteriorly is very common in postobstetric neuropathic faecal incontinence. It is this observation, together with the results of our randomized trial, that leave us in no doubt that total pelvic floor repair is a more logical and successful operation than postanal repair alone.

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Anal endosonography and correlation with *in vitro* and *in vivo* anatomy

Sir
We enjoyed reading the recent article by Mr Sultan and colleagues (*Br J Surg* 1993; **80**: 508–11), which rectified their earlier observation on the endosonographic anatomy of the anal canal[1]. We would like to call attention to the fact that the basic endosonographic appearance of the internal and external anal sphincters using *in vitro* and *in vivo* techniques had previously been reported by us 2 years ago[2,3], even though we did not identify the longitudinal muscle they described.

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1. Law PJ, Kamm MA, Bartram CI. Anal endosonography in the investigation of faecal incontinence. *Br J Surg* 1991; **78**: 312–14.
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3. Tjandra JJ, Milsom JW, Stolfi VM *et al.* Endoluminal ultrasonography defines anatomy of the anal canal and pelvic floor. *Dis Colon Rectum* 1992; **35**: 465–70.

Authors' reply

Sir
We acknowledge the contribution by Drs Milsom and Tjandra to the study of the endosonography of the anal sphincters. This paper was not referenced in our article, which was submitted in April 1992, because the paper by Tjandra *et al.* was not published in *Diseases of the Colon and Rectum* until May 1992. The studies were rather different in methodology. I am sure all authors appreciate the difficulties of altering papers once accepted and understand a reluctance to do so unless the recent publication requires substantial alteration.

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Regional anaesthesia and surgical morbidity

Sir

The question of whether regional anaesthesia in appropriate patients is superior to general anaesthesia has been discussed for many years. In the past decade, at least two well conducted randomized trials of sufficient sample size[1,2] showed that for mortality no benefit is given by regional anaesthesia. Nevertheless, Messrs Scott and Kehlet (*Br J Surg* 1988; **75**: 299–304) claim that 'the large amount of data suggests that (regional anaesthesia) should be used ... whenever possible'. They state, based on their meta-analysis[3], a '30 per cent reduction in early mortality'. If their conclusion were correct, regional anaesthesia would indeed have to be advocated in all appropriate cases.

Unfortunately, Scott and Kehlet give no evidence that it is justified to pool the mortality rates given in the cited papers (*Figure 1* of the publication). No test for homogeneity or heterogeneity was performed. The legend of *Figure 1* suggests that in all cited studies mortality was counted until the 30th day after operation. Unfortunately, this is not the case. The authors give the mortality rate for one cited study[4] until the 14th day, regardless of the fact that, in this study, the mortality is given for each day until the 56th. Regarding another study[5], it was overlooked that five deaths were excluded from comparison because of reinterventions and that the mortality rates cited reflect the first 3 months after operation. A further study[1] gives mortality until the 28th day, not the 30th.

Some of the papers in their meta-analysis included both sexes, others only women. Regional anaesthesia was spinal in one study and epidural in another, and the methods of general anaesthesia used covered the whole spectrum from methoxyflurane to neuroleptanalgesia, from spontaneous breathing by a face mask to controlled ventilation in intubated patients, and nearly all available muscle relaxants. Finally, one study[6] was not randomized, and the sizes of the trials analysed range from 40 to 578 patients.

I wonder whether meta-analysis can be carried out in this way and doubt, until better evidence is given, that 'the large amount of data suggests that (regional anaesthesia) should be used ... whenever possible'. Is it justified to pool mortality rates covering very different postoperative timespans from studies with very dissimilar sample sizes, then to calculate a significant difference ($P < 0{\cdot}01$) and to make such a statement?

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1. Davis FM, Woodner DF, Frampton C *et al.* Prospective multicentre trial of mortality following general or spinal anaesthesia for hip fracture surgery in the elderly. *Br J Anaesth* 1987; **59**: 1080–8.
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Authors' reply

Sir

In our paper we reviewed data from controlled trials at that time and emphasized that a proper meta-analysis could not be performed because of inhomogeneity between the different trials. However, in the case of mortality rates we found it valuable to combine the available results but again without carrying out a proper meta-analysis (for the reasons mentioned). We agree with Professor Link that a few of the authors did not calculate mortality exactly on day 30, but we tried to extrapolate the data as closely as possible to this criterion. We disagree that one of the studies was not randomized[1]; a part of it was randomized, and only that part was included in the Review.

A recent proper meta-analysis of the available data on mortality rates after hip surgery in patients undergoing regional *versus* general anaesthesia[2] supports the conclusion in our paper. The debate continues on the potential advantages of regional *versus* general anaesthesia in surgical procedures. As emphasized by Professor Link, available studies are not directly comparable and therefore hinder exact interpretation. We still find it valuable to draw potential clinical conclusions despite these flaws. We maintain our conclusion that regional anaesthesia should be used whenever possible in patients undergoing hip surgery, based on the morbidity data so far published[3].

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1. Wickström I, Holmberg I, Stefansson T. Survival of female geriatric patients after hip fracture. A comparison of 5 techniques. *Acta Anaesthesiol Scand* 1982; **26**: 607–14.
2. Sorenson RN, Pace NL. Anesthetic techniques during surgical repair of femoral neck fractures. A meta-analysis. *Anesthesiology* 1992; **77**: 1095–104.
3. Kehlet H. General *vs* regional anesthesia. In: Rogers M, Tinker J, Covino B, Longnecker DE, eds. *Principles and Practice of Anesthesiology*. St Louis, Missouri: Mosby, 1993: 1218–34.

Statistical comment

Sir

I tend to agree with the criticisms in Professor Link's letter. The original Review omits a number of crucial details, which makes it very difficult to be confident that the 'meta-analysis' is sound. In particular there is no description of the methods used to identify relevant studies to be included, there is no description of the statistical methods used to combine the studies, and the conventional plot showing the confidence intervals for the relative risk from each study is omitted.

However, it is relevant to point out that the paper was published in 1988, when the art of meta-analysis was less well developed than it is today. Is a debate on this paper relevant, or has it been overtaken by other trials published in the area since 1988?

G. D. Murray

Statistical Consultant
BJS

Pneumothorax during laparoscopic dissection of the diaphragmatic hiatus

Sir

The letter by Mr Reid and colleagues (*Br J Surg* 1993; **80**: 670) highlights the risk of pneumothorax during laparoscopic dissection of the oesophagus. Certainly the proximity of the left pleura mandates careful dissection to avoid puncture with resultant pneumothorax. We agree that conversion to an open procedure is not always required if pneumothorax results.

However, pneumothorax does not always produce hypotension and hypoxia during laparoscopic dissection. A chest drain is not always required, and the operation does not always need to be halted if pneumothorax is suspected so as to confirm the diagnosis by chest radiography and place a chest drain. Also, an insufflation pressure of 15 mmHg is probably excessive. We have found 10 mmHg to be sufficient for laparoscopic oesophageal dissection, reducing the risk of pneumothorax and pneumomediastinum.

During over 80 laparoscopic Nissen fundoplications, we have seen two cases of pneumothorax[1]. A 39-year-old man underwent laparoscopic fundoplication. During dissection of the oesophagus, the left pleura was visibly breached; the anaesthetist was informed of this. As there was no change in the patient's haemodynamic state or oxygen saturation as measured by pulse oximetry, the procedure was allowed to continue uneventfully. At the conclusion of the operation, a chest radiograph was obtained and confirmed a left pneumothorax. A chest drain was placed and removed on the first day after operation.

A 91-year-old man with a huge hiatal hernia and associated gastric volvulus underwent laparoscopic fundoplication with crural repair and anterior gastropexy. Insufflation with carbon dioxide distended a large hiatal hernia sac, enabling good vision of the hiatal structures. During dissection of the oesophagus, however, the left pleura was breached resulting in collapse of the hernial sac from gas entering the left pleural space, obliterating the view within the sac. Again, there was no associated hypoxia or haemodynamic compromise, enabling the procedure to progress uneventfully. Postoperative chest radiography showed pneumomediastinum but no pneumothorax. As carbon dioxide is highly water-soluble, small amounts of the gas in the pleural cavity will be rapidly resorbed.

While we agree with Reid *et al.* that pneumothorax associated with hypoxia and hypotension mandates stopping the operation to confirm the diagnosis, deflate the abdomen and place a chest drain, pneumothorax without associated problems does not require any of these manoeuvres. Postoperative chest radiography is probably sufficient. A small pneumothorax will resorb rapidly; a large pneumothorax is probably best managed by aspiration rather than chest drainage in the first instance.

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1. Jamieson GG, Watson DI, Britten-Jones R, Mitchell P, Anvari M. An initial experience with laparoscopic Nissen fundoplication. *Surg Endosc* 1993; **7**: 234.

Effect of suture material on tumour cell adherence at sites of colonic injury

Sir

We read with interest the article by Mr Reinbach and colleagues (*Br J Surg* 1993; **80**: 774–6) regarding the effect of suture materials on tumour cell adherence at sites of colonic injury and agree with the authors' recommendation that the anastomosis should be created using a suture with a low potential for tumour cell adherence. We feel, however, that previous studies have failed adequately to compare the influence of chemical and structural properties of sutures on tumour cell adherence.

We recently carried out an *in vitro* study on the adherence of malignant cells to suture materials, and compared chemically similar but topographically dissimilar materials and *vice versa*[1]. Significantly more cells adhered to both multifilament and protein-based sutures compared with monofilament and synthetic or metal sutures. Our results suggest that multifilament and protein-based sutures should be avoided to minimize the risk of malignant cell implantation.

C. R. Uff
R. K. S. Phillips

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1. Uff CR, Yui CY, Boulos PB, Phillips RKS. The influence of suture physicochemical and surface topographic structure on tumor cell adherence. *Dis Colon Rectum* 1993 (in press).

Vibration white finger

Sir

I was disappointed to read the Review by Dr Palmer and Mr Collin (*Br J Surg* 1993; **80**: 705–9), which perpetuates the myth that the effects of chronic exposure to vibration are entirely vascular. The Stockholm Conference[1] in 1986 was called specifically to recognize the neurological effects. It was agreed that the condition should be renamed 'hand–arm vibration syndrome' to take account of these symptoms, and the Stockholm Workshop scale[2] was developed to define both vascular and neurological symptoms, and allow for each patient to be so graded. The Review quotes only the vascular part of the scale, so the sensorineural stages are given in *Table 1*.

Table 1 *Sensorineural stages of the hand–arm vibration syndrome*

Stage*	Symptoms
0SN	Exposed to vibration but no symptoms
1SN	Intermittent numbness with or without tingling
2SN	Intermittent or persistent numbness, reduced sensory perception
3SN	Intermittent or persistent numbness, reduced tactile discrimination and/or manipulative dexterity

*The sensorineural stage is established for each hand

I would not agree that common law damages or compensation for hand–arm vibration syndrome is a difficult matter and one that is rarely successful. A large number of cases have been successfully pursued through the courts, while others have been settled for appreciable sums.

The Royal College of Physicians report[3] can be commended for a full review of the condition.

C. L. Welsh

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1. Gemne G, ed. Symptomatology and diagnostic methods in the hand–arm vibration syndrome. *Scand J Work Environ Health* 1987; **13**(Suppl 4).
2. Brammer AJ, Taylor W, Lundborg G. Sensorineural stages of the hand–arm vibration syndrome. *Scand J Work Environ Health* 1987; **13**(Suppl 4): 279–83.
3. Working Party, Faculty of Occupational Medicine of the Royal College of Physicians. *Hand-transmitted Vibration: Clinical Effects and Pathophysiology*. London: Royal College of Physicians, 1993.

Authors' reply

Sir

While it was not our intention to perpetuate any myths, our article concentrated on the vascular effects of chronic vibration exposure because these are the most important in terms of the suffering caused. This is illustrated by the fact that vibration white finger is the disease most commonly responsible for Disablement Benefit payments in the UK.

As regards common law damages for vibration white finger, the National Legal Officer of the General, Municipal and Boilermakers' Union, that perhaps most involved in this matter, agrees that it is an extremely difficult and unpredictable area of litigation and one that is rarely successful (J. O'Hara, personal communication). The principal difficulty is proving that the employer was negligent: this cannot be done in the great majority of cases.

R. A. Palmer

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Return to work after inguinal hernia repair

Sir

We were most interested in the Short Note by Dr Rider and colleagues (*Br J Surg* 1993; **80**: 745–6) on return to work after inguinal hernia repair. We recently carried out a postal questionnaire of 98 local general practitioners (GPs), asking how many days they advise a patient to stay off work after unilateral inguinal herniorrhaphy, using a similar

Table 1 *Times that practitioners advised patients to stay off work*

Type of work	Median (interquartile range) time (days)
Light	28 (21–35)
Moderate	42 (35–49)
Heavy	63 (49–84)

classification for type of occupation. We were surprised at the wide range of responses (*Table 1*).

It is clear that some GPs are considerably more enlightened than others in allowing earlier return to work. Interestingly, 20 per cent of them had some experience of patients who had undergone laparoscopic hernia repair, but only 56 per cent were sending these patients back to work sooner.

These findings reinforce the opinion that GPs are an important factor in delaying return to work after inguinal herniorrhaphy. We feel that it is the surgeon's responsibility to advise the GP and the patient regarding early return to work, and this may be especially important with regard to the laparoscopic technique, with which few GPs are yet familiar.

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Announcement

The British Journal of Surgery Society SRS Prize

The British Journal of Surgery Society is to make a generous annual donation of £500 to the Surgical Research Society to be used as a prize. The Committee of the SRS, on behalf of its membership, is pleased to acknowledge the gift with gratitude.

The SRS Committee has decided that the prize will be awarded for the best paper published in the *BJS* that originates from an SRS presentation in the preceding year. The Committee of the SRS will judge these papers at its January meeting and the prize will be announced and presented at the dinner of the SRS.

The SRS is pleased to maintain close ties with the Journal. Two months each year are special SRS issues and contain most of the papers from presentations made to the SRS. It is hoped that this prize will encourage more presenters of SRS papers to prepare manuscripts without detracting from the principle of the SRS to enjoy receiving reports of work in progress. Papers not making publication in the SRS issues *will not be ineligible* and the winner of the Patey Prize *may* submit a paper and be equally eligible. It should be noted that any paper submitted as a result of presentation to the SRS passes through the same rigorous process of referee analysis and editorial criticism by the Journal; publication is not guaranteed.

SRS authors should identify the January or July meeting of the presentation on the submitted manuscript. Papers will automatically be collected and reviewed for the prize. Those already published in 1993 issues will automatically be included for consideration of the prize to be awarded for the first time in January 1994.

'Thank you' to The British Journal of Surgery Society for fostering and encouraging surgical research.

J. R. Farndon

Book reviews

Current Surgical Practice

M. Hobsley, A. Johnson and T. Treasure (eds). 232 × 155 mm. Pp. 203. Illustrated. 1993. Sevenoaks, Kent: Edward Arnold. £32·50.

The sixth edition of this popular series maintains the traditions of its predecessors, highlighting the areas of growth and change in surgical practice. The present volume is arranged in two parts, the first a report of a symposium on decision making in surgery, the second invited contributions from experts.

The symposium encompasses articles on rational decision making in surgical practice, and the timing and rationale for the withholding or withdrawal of medical treatent. Audit, a most topical issue, is dealt with by a broad-ranging article that presents not only the methodology of audit but the rationale for it and the likely patient benefits to be achieved by it. The benefits and resource implications of day surgery, presently being encouraged by the Royal Colleges and Health Authorities, are presented in a balanced fashion, stressing the necessity of adequate patient selection and resourcing of the venture.

The invited contributions include a review of the management of gallstone disease, including an appraisal of the latest technological advances. The palliative approach to the treatment of oesophageal cancer, presenting largely the South African experience, favours either surgery or radiotherapy and somewhat dismisses the value of intubation, laser treatment or chemotherapy, conclusions that are unlikely to be universally accepted. Infective and non-infective complications in the immunosuppressed surgical patient are reviewed, as are current advances in the flap technology of plastic and reconstructive surgery. The management of hand injuries is clearly and concisely presented, and a further article ably overviews the pathological and clinical features of spinal cord compression.

The difficulties of keeping up to date with advances in specialties outwith one's own are made less onerous by a volume such as this. The popularity of this series testifies to its value to the generalist and to those approaching examinations in a variety of disciplines.

A. Clason

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Modern Concepts in Surgery

S. K. Srivastava (ed.). 280 × 216 mm. Pp. 494. Illustrated. 1992. New Delhi: McGraw-Hill. US$24·95.

This is a surprising book. The first surprise is that it runs to 494 pages yet costs only US$24·95. The second surprise is that it originates from India and is intended as a practical guide 'to assist surgeons working under varying degrees of limitations and sophistication'. Given the state of the world, producing such a practical guide at modest cost seems highly commendable. So, does it achieve the stated aims?

The first chapter on modern imaging techniques gets the book off to an unfortunate start given the disparaging remarks that are made about reliance on high-tech non-invasive diagnosis in the preface. Sadly, this inconsistency is present throughout. Expensive modern techniques, such as imaging and parenteral nutrition, are described in some detail without trying to assess their strengths and weaknesses in the context of healthcare in the developing world. The chapter on endoscopy devotes a surprising amount of space to descriptions of proctoscopy and rigid sigmoidoscopy. By contrast there is only a rather superficial account of diagnostic laparoscopy, which can be performed with simple equipment and which has considerable application when resources are limited.

Even if the book does not achieve its aim it is still a reasonable surgical text and a bargain at the price. I would not recommend it for trainees in the UK, but it will probably sell well in many other countries.

J. Bancewicz

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UK

Pancreatic Fistulas

P. Pederzoli, C. Bassi and S. Vesentini (eds). 235 × 154 mm. Pp. 212. Illustrated. 1992. Heidelberg: Springer. DM 168.

My attitude to conference proceedings is usually less than enthusiastic, but this volume does constitute an exception. The authors have selected a topic that, although narrow and specialized, nevertheless constitutes a difficult problem that is often poorly treated.

This volume covers the anatomy, physiology, pathogenesis, diagnosis, and medical and surgical treatment of pancreatic fistula in great detail. The authorship is truly international and very authoritative. The book is well printed and well illustrated. While most of the contributions review specific aspects of pancreatic fistula, such as 'Pancreatic fistulas in chronic pancreatitis', 'Pancreatic fistulas in pancreatic transplantation' and so on, there are sufficient original data and anecdotal material to make this a useful volume for the practising surgeon or gastroenterologist. It certainly deserves a place in the library of most large hospitals and constitutes a valuable asset to the surgeon or gastroenterologist with an interest in pancreatic disease.

M. J. McMahon

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Imaging for Surgeons

D. Lisle. 251 × 189 mm. Pp. 296. Illustrated. 1993. Sevenoaks, Kent: Edward Arnold. £65.

This is an excellent hardback reference book that should appeal to both surgeons in training and established consultants. The text is clearly laid out, succinct, yet reasonably comprehensive. The bulk of the book is full of radiographs and images from computed tomography (CT) and magnetic resonance imaging (MRI); some are excellent but unfortunately the quality of reproduction is somewhat variable. The book covers a wide range of surgically related topics, including abdominal trauma, postoperative complications and investigations of the skull and face, and these should be valuable to the surgeon in training. The information provided on the interpretation and relative merits of ultrasonography, CT and MRI will appeal to all. Particularly valuable are the recommendations for a particular investigation in specific circumstances (e.g. MRI rather than CT or *vice versa*). This book fulfils a useful function, bridging radiology and surgery, and would be a valuable asset to a surgical library.

L. Hands

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International Surgical Practice

D. J. Leaper and F. J. Branicki (eds). 240 × 160 mm. Pp. 415. Illustrated. 1992. Oxford: Oxford University Press. £27·50.

As international travel becomes ever more commonplace and migration of people from one part of the world to another increases, it behoves the surgeon to become familiar with conditions not normally seen in everyday practice. This book provides a series of 21 articles that update the reader on topics as diverse as head injury, hepatocellular carcinoma and the surgical management of tropical disease in Asia. The editors have chosen an impressive and international list of contributors who generally write with authority from large personal experience. Some contributions particularly stimulated my interest. Professor Huang from Beijing gives a very succinct account of 1874 patients with squamous carcinoma of the oesophagus treated at his institute. A method of treating gastric cancer using 'immunochemosurgery' is described by Professor Jin-Pok Kim from Seoul showing good 5-year survival figures. The very large experience of managing patients infected with human immunodeficiency virus at Lusaka, Zambia, makes the article written by Professor Bayley and colleagues essential reading.

Although I thoroughly enjoyed reading this book, some of the illustrative material was disappointing. The quality of the operative photographs in the first chapter on 'Tropical diseases in Asia' is poor, as is some of the ultrasonographic hard copy in the same article. I enjoyed reading the account of 'Surgery of the parotid: how I do it', but would question the wisdom of including 16 black and white operative and clinical photographs when line diagrams would have served the purpose much better. Despite these caveats the book is well worth purchasing whether you are a trainee or an established surgeon. My copy is already well used.

A. Munro

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Tutorials in Clinical Surgery in General. Vol. 2

F. G. Smiddy. 215 × 137 mm. Pp. 403. Illustrated. 1993. Edinburgh: Churchill Livingstone. £22·50.

Tutorials in Clinical Surgery in General is the second unreferenced and unindexed text targeted at pre-Fellowship trainee surgeons. It aims to provide tutorials in 32 topics and very largely succeeds. The book is succinct, authoritative yet hugely readable, which must be a godsend for the tired registrar preparing for examinations late into the night. The amount of detail is somewhat variable, doubtless reflecting the author's personal interest. At the risk of nit-picking I thought the paragraph describing the medical treatment of bladder outflow tract obstruction merited expansion and I would expect the Fellowship candidate to have a more detailed understanding of ductal carcinoma *in situ* of the breast and the management of benign breast disease than can be found in these pages.

In summary, this book provides a superb range of surgical topic tutorials written by an experienced examiner and justifies its publisher's claim to be essential reading for the Fellowship candidate. At a cost of £22·50 it is also excellent value.

P. A. Jones

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Updates in Colo-Proctology

J.-C. Givel, G. D. Oates and J. P. S. Thomson (eds). 234 × 154 mm. Pp. 251. Illustrated. 1992. Heidelberg: Springer. DM 138.

Papers on a wide variety of topics are summarized and grouped into sections covering surgical technique, cancer, inflammatory bowel disease and the complications of surgery. These papers vary greatly in their scientific content. Some are anecdotal reports of a few interesting cases, while others are substantial scientific works – such as 'Endoscopic diagnosis of anal intra-epithelial neoplasia', which suggests important parallels in the pathogenesis of anal neoplasia with that of neoplasia of the cervix. The morbidity associated with restorative proctocolectomy is reported in several papers but appears not to have dimmed the enthusiasm of its protagonists. Excellent round-table discussions of management of rectal cancer and complex fistula *in ano* make interesting reading.

This small publication of proceedings of a meeting held in 1990 is of variable quality and difficult to recommend unreservedly to either the Fellowship candidate or the established coloproctologist. It would be interesting to pick up in the library to browse through.

S. T. D. McKelvey

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Publisher's note

Colon and Rectal Surgery. 3rd ed.

M. L. Corman. 260 × 207 mm. Pp. 1328. Illustrated. 1992. Philadelphia, Pennsylvania: J. B. Lippincott. £175.

The review of the above book in the July issue (*Br J Surg* 1993; **80**: 948) incorrectly described Dr Marvin L. Corman as its editor. The publisher, J. B. Lippincott, has asked *BJS* to point out that, with the exception of one small section, the book is written exclusively by Dr Corman.

The Journal apologizes for this error.

Notices and announcements

1–5 November 1993
Annual Course in Hepatobiliary and Pancreatic Surgery
London, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

3 November 1993
Fourth Annual Rush Symposium on Transplantation – Applications of Advancing Technology in Contemporary Hepatology
Chicago, Illinois, USA
Information: Patricia Michaels, Rush Transplant Programs, 1653 West Congress Parkway, Room 201 Jones, Chicago, Illinois 60 612-3833, USA

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

18–19 November 1993
Vascular Surgical Society of Great Britain and Ireland Annual Meeting
Manchester, UK
Information: Mr P. L. Harris, VSS Secretary, Link 8c, The Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP, UK

18–20 November 1993
Combined Meeting of the European Conference on General Thoracic Surgery and 2nd Annual Meeting of the German Society for Thoracic Surgery
Heidelberg, Germany
Information: Administrative Secretariat, c/o AKM Congress Service GmbH, Obere Schanzstraße 18, D-79 576 Weil am Rhein, Germany

30 November to 2 December 1993
Eighth International Workshop on Therapeutic Endoscopy
Hong Kong
Information: Dr S. C. S. Chung, Combined Endoscopy Unit, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong

3 December 1993
Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

6–7 January 1994
Surgical Research Society Meeting
London, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

21–26 January 1994
Introduction to Molecular and Cellular Research
Orlando, Florida, USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20 814-3398, USA

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12 203 Berlin, Germany

14–18 February 1994
Controversies and Recent Advances in Surgical Pathology
San Diego, California, USA
Information: Armed Forces Institute of Pathology, Education Division, Washington, DC 20 306-6000, USA

21–23 February 1994
Seventh Annual Congress of the North American Society of Phlebology on the Advances in Medical and Surgical Treatment of Venous Disorders
Wilea, Hawaii, USA
Information: North American Society of Phlebology, 523 Encinitas Boulevard, Suite 108, Encinitas, California 92 024, USA

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

28–29 March 1994
Injury Research Group Meeting
Swindon, UK
Information: Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, Oxford Road, Manchester M13 9PT, UK

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20 040-030 Rio de Janeiro, Brazil

26–28 May 1994
Surgical Infection Society of Europe 7th Annual Meeting
Vienna, Austria
Information: Professor F. Schulz, c/o Wiener Medizinische Akademie für Ärztliche Fortbildung, Alser Straße 4, A-1090 Vienna, Austria

2–6 July 1994
XVth Biennial Congress of the International Society of University Colon and Rectal Surgeons
Singapore
Information: ISUCRS XVth Congress Secretariat, c/o Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 0316

7–8 July 1994
Surgical Research Society Meeting
Glasgow, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1994
VIIIth Edmondo Malan International Surgery Days – Difficult Surgical Problems
Parma and Colorno, Italy
Information: Professor G. C. Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43 100 Parma, Italy

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW, Suite 300, Washington, DC 20 005, USA

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to: The Senior Editor, *The British Journal of Surgery*, Blackwell Scientific Publications Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 071-404 1831. Facsimile: 071-404 1927.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

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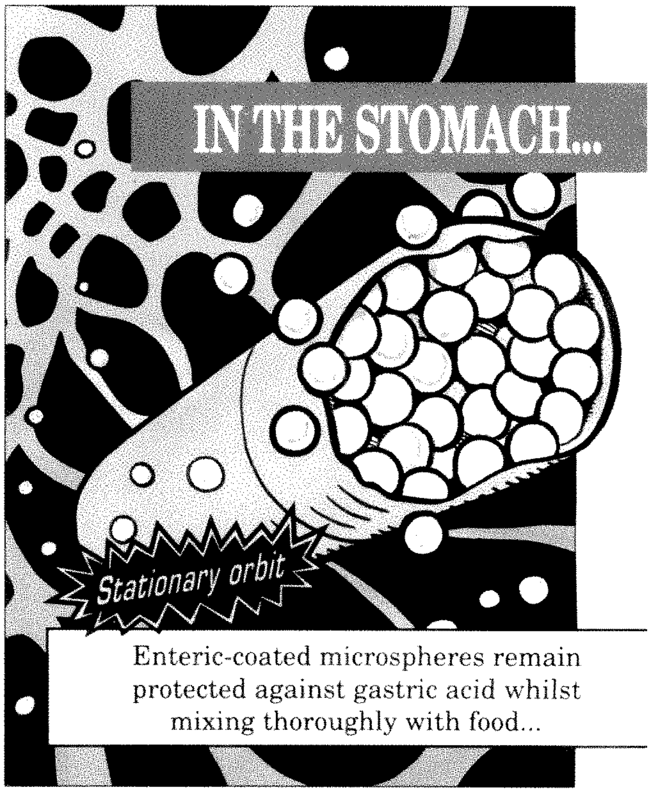

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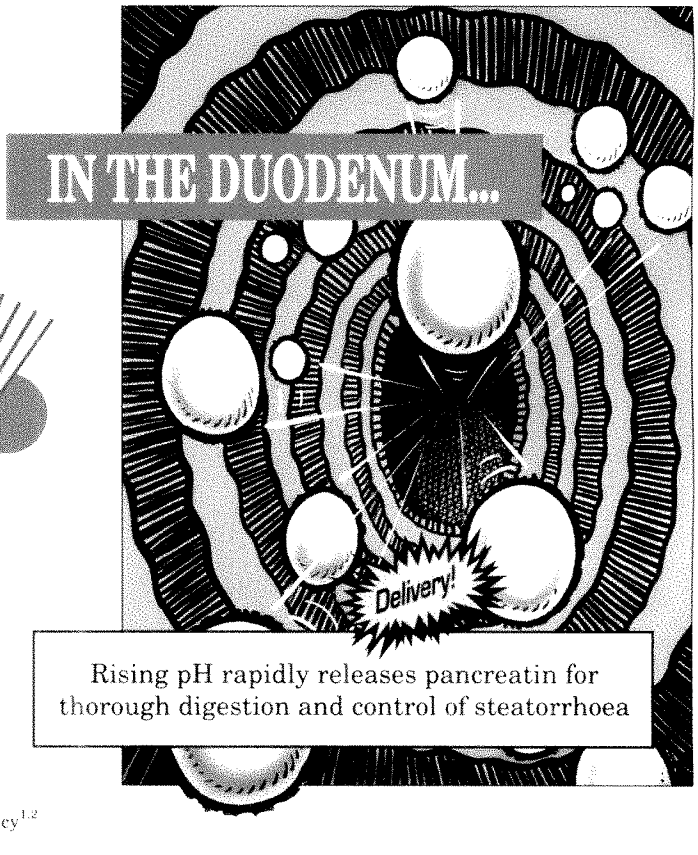

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2. Beverley D W et al. *Arch Dis Child* 1987, **62**, 564-68

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Edited by R J Nicholls, D C C Bartolo and N J Mortensen

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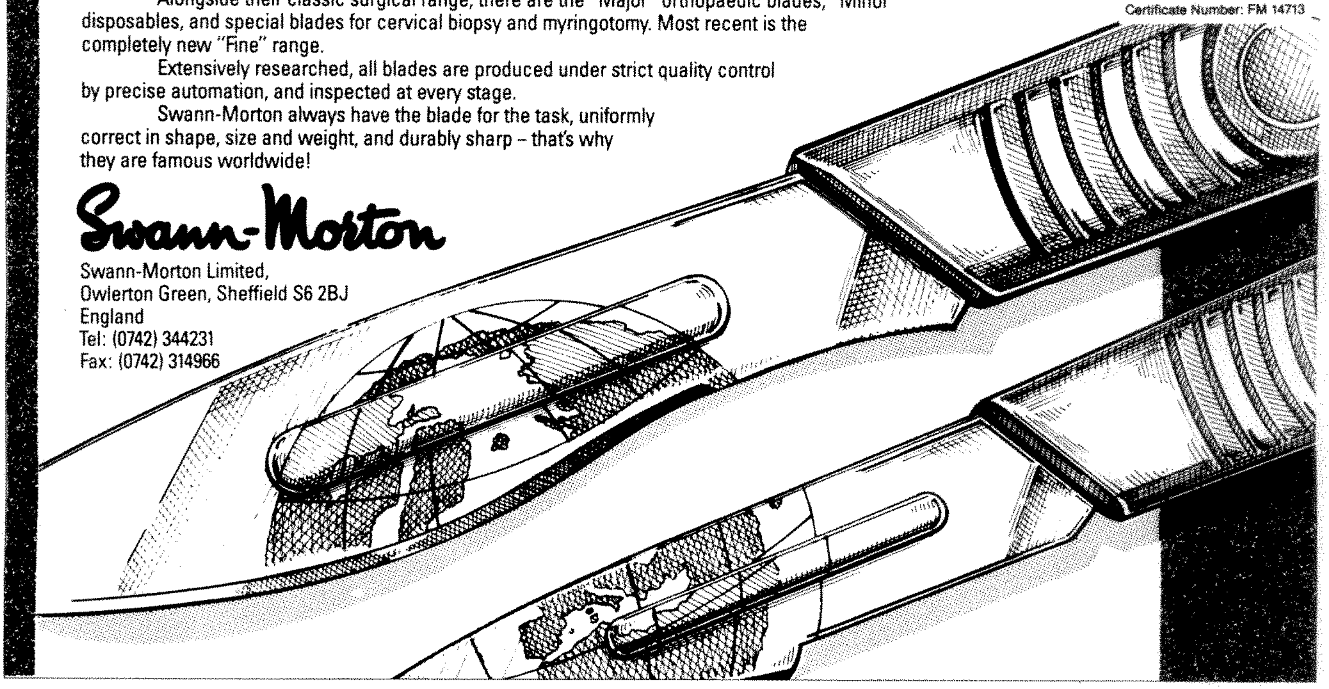

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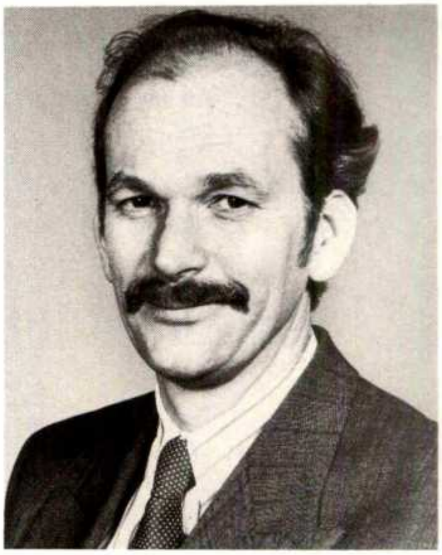

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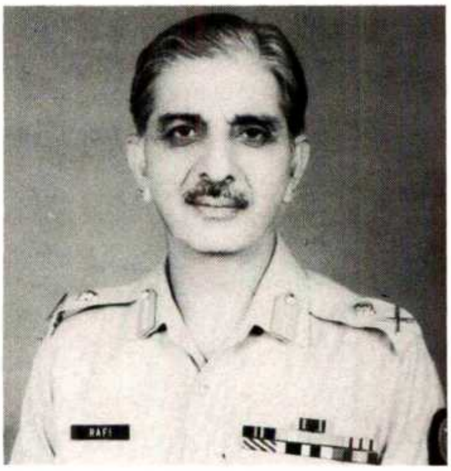

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Robin Williamson

Br. J. Surg. 1993, Vol. 80, November, 1363–1364

Screening for abdominal aortic aneurysm

Ultrasonographic screening for abdominal aortic aneurysm (AAA) reveals a prevalence in men of 2·6 per cent in those aged 60–64 years (J. Hamer, personal communication), 6 per cent[1] at age 65–74 years and 9 per cent[2] in those over 75 years. In women the disease is less common and the age of onset 10–15 years later. The male:female risk ratio[3] of death from ruptured AAA is 11:1 at age 60–65 years, decreasing to 3:1 at 80–85 years. Three groups at increased risk of developing aortic aneurysm have been identified: patients with symptomatic occlusive arterial disease, cigarette smokers, and first-degree relatives of patients with AAA. For men with intermittent claudication or coronary artery disease the relative risk is two to three times that of the general population, while for first-degree male relatives of patients with aneurysm the risk is increased fivefold[4].

The ideal screening programme for AAA would focus resources on an easily identifiable population old enough to have developed the disease but young enough to benefit from prophylactic surgery. The Gloucestershire community screening programme[5] for AAA is now screening men in their 65th year. At this age the prevalence of aneurysm 3·0 cm or more in diameter is 4·4 per cent and of those 4·0 cm and over 1·3 per cent. As all majestic oak trees from little acorns grow, so all clinically significant AAAs develop from small aneurysms detectable only by scanning. The growth rate of small aortic aneurysms is generally slow but accelerates as they increase in size. For those under 4·0 cm in diameter[6] the average growth rate is 0·2 cm per annum, while 6·0-cm aneurysms[7] grow at a mean of 0·5 cm per annum. Follow-up studies[6] on small AAAs have shown that 89 per cent grow less than 0·6 cm a year. Consequently, the smallest aneurysms detectable ultrasonographically are unlikely to reach a size at which most surgeons would recommend elective repair for at least 5 years. It follows that interval screening of men found not to have an aneurysm at 65 years is unlikely to be worth while until they have lived to three score years and ten. Large aneurysms grow quickly and rupture while small aneurysms grow slowly and usually do not, so inevitably most AAAs detected by screening are small. There is universal agreement that for an aneurysm of 5·5 cm or more in diameter elective surgical resection confers the best protection against premature death, even though the average operative mortality rate in the UK is likely to be nearer 8 per cent than the 4 per cent or less reported from some specialist units[8]. For patients with aneurysms of 4·5–5·4 cm there is general uncertainty whether survival beyond 12 months is more likely to be achieved by elective surgical correction or conservative management. Prospective randomized trials to resolve this doubt are currently in progress in Canada, the UK and the USA, with the latter two trials also including aneurysms of 4·0–4·4 cm diameter.

Fewer than 0·5 per cent of men aged 65 years will have an AAA 5·5 cm or more in diameter detected by prevalence screening, but a further 1–2 per cent will have smaller aneurysms that can be expected to grow to this size within 5 years. If one assumes that the annual incidence of aortic aneurysm 5·5 cm or more in diameter is 0·4 per cent in the 65–74 years age group, then screening men aged 65 years with interval ultrasonography at 70 years would render 40 patients aged 65–74 years per 10 000 per annum liable to elective aneurysm repair. Currently 13 men per 10 000 per annum in this age group in Oxford undergo elective and emergency surgery for AAA of at least 5·5 cm diameter. Even allowing for the 60 per cent of patients with aortic rupture who die at home or before surgery, there is still an annual discrepancy of 18 aneurysms per 10 000 at-risk population. What happens to almost half of all those with a large aortic aneurysm is unknown. Some will survive well into their eighth decade of life with a large intact aneurysm, others will die from unrelated natural causes. Some, no doubt, will die from unrecognized aneurysm rupture recorded for posterity as yet another death from myocardial infarction.

There is now no doubt that screening men at 65 years or more with abdominal ultrasonography will reveal many unsuspected AAAs; some will be clinically significant on detection and most will become so over the following decade. The fundamental question that remains unanswered is: Does it do any good? As with

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screening for breast cancer this question can ultimately be answered only by a well organized randomized multicentre trial with follow-up to death. The weak link in any such study will be the unreliability of certified causes of death. In many cases unless autopsy is performed the recorded cause of death is little more than an inspired guess. It is likely that in screened patients known to have AAA the guess will include ruptured aneurysm, while in unscreened controls with an occult aneurysm it will not. Unless this problem can be satisfactorily resolved there is a danger that even a substantial benefit conferred by screening for aortic aneurysm will go unrecognized.

Without a screening programme there is still much that could be done to reduce the incidence of ruptured aortic aneurysm. Craig *et al.*[9] have shown that in the 2 years before aortic rupture one-quarter of patients with aneurysm had been diagnosed but most were not referred to a vascular surgeon. A further 38 per cent of patients had undergone medical examination without the aneurysm being noticed. Opportunistic screening of the aorta in elderly men presenting with other illness might achieve almost as much as a formal screening programme if the diagnosis of AAA always occasioned referral to a vascular surgeon.

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Br. J. Surg. 1993, Vol. 80, November, 1365–1367

Surgical options for primary hepatocellular carcinoma

Hepatocellular carcinoma (HCC) accounts for more than 1 million deaths each year worldwide and even quite small tumours, untreated, confer a poor prognosis – fewer than 13 per cent of patients are alive at 3 years[1]. Many patients with HCC will have chronic liver damage resulting from hepatitis B or C, and cirrhosis in more than three-quarters makes surgery hazardous. In advanced cases, only palliation with chemotherapy is possible. Tumour irradiation, alcohol injection and cryotherapy are current treatment options being explored. Transarterial catheter embolization has also been advocated and a 1-year survival rate of 50–78 per cent reported[2,3]. Nevertheless, complete tumour resection offers the only realistic prospect of cure. Should such liver resection be partial – or complete and followed by hepatic transplantation?

In the absence of cirrhosis, resection is the treatment of choice and can be undertaken with low morbidity and a hospital mortality rate of 3–15 per cent. The 5-year survival rate of patients with tumours less than 2 cm in size is high, although this decreases to between 20 and 37 per cent[4] when the tumour size exceeds 5 cm. Extended hepatic resection of tumours with major vascular invasion has been reported and results may be improved by preoperative chemotherapy. Complete hepatic excision followed by transplantation should be reserved for the relatively few non-cirrhotic patients who have cancer of all the major compartments of the liver but for whom staging indicates that malignancy is confined to this organ.

The surgical approach in patients with cirrhosis is less clearly defined. Resection rates are low with advancing or decompensating liver disease (Child's grade B or C) in which the risk of haemorrhage, infection and liver decompensation is significant. The degree of parenchymal hepatic reserve in patients with cirrhosis may be established by assessing synthetic function by measuring the serum albumin level and prothrombin time, as well as by standard liver function tests; bromsulphthalein or indocyanine green clearance may be included. Resection in patients with Child's grade B or C cirrhosis is usually confined to tumours less than 5 cm in size situated peripherally, which can be removed by non-anatomic or segmental excision, maximizing the residual liver mass. In such cases, mortality rates are below 10 per cent, but it is important that an adequate tumour clearance margin of at least 1 cm is achieved if local recurrence is to be avoided.

Patient survival frequently depends not only on the likelihood of tumour recurrence but also on the underlying stability of the cirrhosis. Progression of cirrhosis means that fewer than 30 per cent of patients with Child's grade B or C disease will avoid complications of variceal haemorrhage or hepatic decompensation. The 5-year survival rates are low (0–23 per cent)[5,6] because as many patients succumb to progression of cirrhosis as to recurrent tumour. Larger tumours or those situated more centrally may be irresectable because of inadequate hepatic reserve and even with modern surgical techniques mortality rates increase. Nagasue *et al.*[6] reported a 3-year survival rate of only 16 per cent in patients under 60 years of age with Child's B or C cirrhosis and tumours less than 5 cm in size or in those with multicentric HCC nodules. Such patients, they concluded, should be considered for transplantation.

The high rate of recurrence that marked the early disappointing results of transplantation was often the result of advanced tumour stage, with residual cancer in coeliac lymph nodes in a high proportion of patients; fewer than 20 per cent of such patients survived more than 2 years. However, Ringe *et al.*[7] showed that when coeliac nodes did not contain tumour approximately half of all patients survived for more than 3 years after transplantation.

In the European Liver Transplantation Registry[8], the 3-year survival rate of patients after transplantation for HCC is over 40 per cent, although this figure includes 'incidental' tumours. An attempt to address the issue of residual lymph node disease led previously to radical hepatic excision and *en bloc* clearance of the coeliac lymph nodes and adjacent tissue before transplantation – the so-called 'cluster' operation[9]. These complex procedures were largely abandoned when it became clear that the 2-year survival rate was less than 20 per cent in patients whose coeliac lymph nodes contained tumour[10]. In patients with negative lymph nodes (and so presumably not requiring such a wide radical foregut excision) the 2-year survival rate was more than 70 per cent, not significantly different from that of patients undergoing 'simpler'

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hepatic transplantation[11]. In the light of this re-evaluation of the early experience of transplantation for HCC, meticulous cancer staging is now undertaken in patients with Child's grade B or C cirrhosis.

In south-east Asia small tumours less than 5 cm in size are routinely resected in compensated patients with Child's grade A cirrhosis and, provided that adequate tumour clearance is achieved, with good results. A 5-year survival rate of between 25 and 67 per cent has been reported[4], although tumour recurrence or the development of new multicentric HCC requires further treatment in some patients. Most Asian patients have non-alcoholic liver disease and some reports have included those with hepatitis who may not be cirrhotic. Indeed, Child's grades such as 'functional' A or B may be related to indocyanine green clearance and may be used in patients for whom histological analysis does not show cirrhosis. Parenchymal hepatic function in such patients may be good[4,6], with a normal coagulation profile and concentrations of bilirubin and albumin, and an indocyanine green clearance rate of over 85 per cent at 15 min. The results of HCC excision are good, with a low hospital mortality rate and 52·7 per cent of patients alive at 3 years. Even so, only 25 per cent of patients[6] survive to 8 years.

In many Western countries hepatitis B is less common and the Child classification is usually restricted to those with histologically confirmed cirrhosis, in whom outcome may be less certain. Among such patients a peripheral HCC less than 5 cm in diameter is rare and for centrally situated or large tumours the morbidity and mortality rates have been high when hemihepatectomy has been undertaken. The progression of cirrhosis in conditions such as haemochromatosis, chronic active hepatitis, primary biliary cirrhosis and alcoholic liver disease means that the risk of hepatic decompensation is significant. The uncertain prognosis of the underlying parenchymal liver disease combined with concern about recurrent or metachronous HCC, especially if inadequate tumour clearance occurs, has led to reappraisal of the benefits of complete hepatic resection and transplantation[12].

With improvements in immunosuppression and modification of the surgical techniques of hepatic transplantation, many elective patients can receive grafts safely with low morbidity, a mean hospital stay of less than 20 days and a hospital mortality rate under 8 per cent. Recent analysis of patients with cirrhosis and comparable tumour stage gave a 5-year survival rate of 35·6 per cent for those who underwent complete hepatic resection and transplantation, compared with no survivors among patients who had partial hepatectomy[11]. The use of neoadjuvant chemotherapy in patients receiving grafts for HCC may allow a wider selection of patients. One recent study[13] reported that 59 per cent of patients were alive at 3 years with 54 per cent disease-free when concomitant neoadjuvant chemotherapy was used. In over half of these patients the tumour size was greater than 5 cm.

Complete hepatic excision with liver transplantation is not appropriate for all patients with cirrhosis and careful assessment is needed, especially when alcoholic cirrhosis is the underlying disease. Against the benefits of transplantation must be balanced its significant cost, the need for life-long immunosuppression and the relative shortage of donor organs. Moreover, hepatitis B may recur in the grafted liver, in spite of hyperimmune globulin. While the option of transplantation is not appropriate for elderly patients with concomitant major disease, it should be considered for those of less than 60 years with underlying cirrhosis and a large central tumour or multifocal disease.

It is likely that in the immediate future the approach to the treatment of HCC in different countries will vary. In south-east Asia, where for cultural reasons cadaveric organ donation is not common and transplantation is rarely possible, skilled clinical teams will continue to achieve good short-term results using resection for small peripheral HCC in patients with mildly compromised hepatic function. Elsewhere, for patients with HCC and cirrhosis management protocols will increasingly include the complete range of options, both surgical and oncological, adding complete liver excision and transplantation to the standard technique of partial hepatectomy. Only by combining screening and earlier diagnosis of HCC with a wider range of complementary surgical options will the prognosis of this condition be improved.

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Review

Br. J. Surg. 1993, Vol. 80, November, 1368–1373

Hepatocyte growth factor/scatter factor, liver regeneration and cancer metastasis

Hepatocyte growth factor (HGF) is the most potent stimulator of hepatocyte growth and DNA synthesis identified; it is now known to be the same molecule as scatter factor, which increases the motility of a variety of cell types. HGF is becoming recognized as one of the most important factors in the regulation of liver regeneration after surgical resection or chemical damage. HGF is produced by several tissues, including neoplasms; it can therefore provide a stimulus for increased motility of malignant cells by both a paracrine and autocrine mechanism. The receptor for HGF has been identified as the product of the oncogene c-met, *raising the possibility that this gene plays a key role in facilitating cellular invasion. HGF may therefore be important not only for liver cell growth but also in metastasis. This article summarizes the current position of research on HGF, and presents both clinical and scientific evidence that strongly implicates this factor in liver regeneration and cancer invasion and metastasis.*

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Discovery of hepatocyte growth factor

The appearance of novel proteins in the blood after liver resection has long been recognized. However, it was not until 1984 that the existence of a specific factor that triggered liver regeneration was defined. This factor was isolated in a partially purified form from rat plasma after partial hepatectomy by Nakamura *et al.*[1], who termed it hepatocyte growth factor (HGF). In the same year, Michalopoulos *et al.*[2] reported two serum factors related to liver regeneration, and Russell and colleagues[3] partially purified a factor from rat platelets. It was later established that these factors, named hepatopoietin A[2,4] and tumour toxic factor[5] respectively, were the same as HGF.

By 1989, HGF had been fully purified, its amino acid sequence determined and the encoding complementary DNA (cDNA) cloned[4,6,7]. HGF is derived from a single-chain precursor of 728 amino acids and processed into two peptide chains (α and β) with apparent molecular weights of 69 and 34 kDa. Its gene is located on chromosome 7, and contains 18 exons and 17 introns.

Hepatocyte growth factor and scatter factor are the same molecule

In 1985, a fibroblast-derived factor that had major effects on cell motility was described. It was named scatter factor (SF) by Stoker and Perryman[8] because it had the ability to 'scatter' tightly growing cell colonies. The factor contained heavy and light subunits with apparent molecular weights of 58 and 31 kDa. Partial amino acid sequencing revealed more than 90 per cent identity with both rat and human HGF[9,10].

The cDNAs encoding HGF and SF are the same[11] and antibodies raised against each factor recognize the other[12]. Since the factors have identical biological activities and receptors[13], most workers now refer to the molecule as HGF/SF. For convenience the factor will be referred to as HGF in this review.

Biological activity of hepatocyte growth factor

HGF has biological effects on various cell types (*Table 1*). It is recognized as the most potent stimulator of DNA synthesis in hepatocytes in primary culture. However, in contrast to normal hepatocytes, the growth of a number of hepatoma cell lines is inhibited by HGF[14,15,25]. The reason for this striking difference is not clear. Okano and colleagues[26] recently showed that the intracellular signal for HGF stimulation in these two types of cell is different; HGF induced tyrosine phosphorylation of phospholipase C_γ in normal hepatocytes but no such change was noted in hepatoma cells. HGF also regulates other functions of hepatocyte and hepatoma cells, such as acute-phase protein synthesis and α-fetoprotein production[27,28].

HGF is also a potent stimulator of cell motility. Although the canine kidney epithelial cell line MDCK is often used experimentally to demonstrate increased cell motility after treatment with HGF, a variety of other cell types also respond in a similar way, including those that are important to surgeons, such as colonic cancer cells[19], hepatoma cells and gastric adenocarcinoma cells[16]. Scattering of cell colonies is pronounced with HGF; several methods including basement membrane invasion, dissociation of carrier beads and time-lapse cinematography have been used to demonstrate that HGF increases cell motility. The increased motility may be related to changes in the cytoskeleton (for example involving F actin, myosin or vimentin[29]) or to changes of E cadherin in target cells[30].

Other properties of HGF include stimulation of haematopoietic cell growth, synergism with other cytokines[31] and 'priming' neutrophils for the oxidative response[32].

Production of hepatocyte growth factor

Many different cell types produce HGF including Kupffer cells[33], endothelial cells[33], fibroblasts[34,35], fat-storing cells in the liver[36,37], endothelial cells in the lung[38,39], HL-60 myelomonocytic cells[40] and some malignant cells, including those of lung and pancreatic carcinoma[38,41]. Expression of HGF in other normal and malignant tissues has also been reported[42,43]. Among normal tissues pancreas, small intestine, thyroid, brain and submaxillary salivary gland produce and express high levels of HGF; liver, kidney and spleen produce undetectable amounts.

The regulation of HGF production remains the subject of

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Table 1 *Effects of hepatocyte growth factor on cell motility and growth*

Reference	Cell type	Motility	Growth
Tajima *et al.*[14]	Hepatocyte	?	+
Tajima *et al.*[14]; Shiota *et al.*[15]	Hepatoma	+	−
Shibamoto *et al.*[16]	Gastric cancer	+	+
Tajima *et al.*[14]; Matsumoto *et al.*[17]	Keratinocyte	+	+
Tajima *et al.*[14]; Matsumoto *et al.*[18]	Melanocyte	+	−
Tajima *et al.*[14]	Melanoma	?	−
Jiang *et al.*[19]	Colonic cancer	+	−
Tajima *et al.*[14]	Lung cancer	+	+
Morimoto *et al.*[20]	Microvascular endothelial cells	+	+
Gherardi and Stoker[10]; Kan *et al.*[21]	Kidney epithelial cells	+	+
Bussolino *et al.*[22]; Rosen *et al.*[23]	Endothelial cells	+	+
Joplin *et al.*[24]	Biliary epithelial cells	?	+

Table 2 *Hepatocyte growth factor receptor/c-*met *expression*

Reference	Tissue type	Receptor expression	Receptor study method
Miyazawa *et al.*[7]	Hepatocyte	+	Northern blotting, immunostaining
Prat *et al.*[57]	Hepatoma	+	Northern blotting, immunostaining
Tajima *et al.*[14]	Hepatoma	+	Western blotting, binding assay
Di Renzo *et al.*[58]; Kuniyasu *et al.*[59]	Gastric cancer	+	Northern and Western blotting
Jiang *et al.*[19]; Prat *et al.*[57]; Di Renzo *et al.*[58]; Liu *et al.*[60]	Colonic cancer	+	Northern and Western blotting
Tajima *et al.*[14]	Kidney and spleen	+	Western blotting, binding assay
Prat *et al.*[57]	Keratinocyte	+	Northern blotting, immunostaining
Tajima *et al.*[14]; Halban *et al.*[61]	Melanocyte, melanoma	+	Western blotting
		+	Western blotting, binding assay
Di Renzo *et al.*[62]	Thyroid cancer	+	Western and Northern blotting
Katyal *et al.*[63]	Lung	+	Northern blotting
Tajima *et al.*[14]	Lung cancer	+	Western blotting, binding assay
Rygaard *et al.*[64]	Lung cancer	+	Northern blotting
Di Renzo *et al.*[58]	Leukaemia, lymphoma	−	Northern and Western blotting
Tajima *et al.*[14]	Fibroblast	−	Western blotting, binding assay
Tajima *et al.*[14]	Haematopoietic cells	−	Western blotting, binding assay

intense research, but some factors that may affect this production (or messenger RNA (mRNA) expression) have been identified. 'Injurin' is a 10–13-kDa circulating protein whose level increases markedly in blood after organ injury and is a potential stimulus for HGF production[39]. HGF production and gene expression are also triggered by interleukin (IL) 1α and 1β[44], whereas both production and gene expression of HGF by fibroblasts are inhibited by transforming growth factor (TGF) β[36,45,46].

The pharmacodynamics of HGF *in vivo* are not clear. It has been reported that the factor is removed from the circulation by the liver and that both a receptor-mediated and a non-specific internalization are involved[47,48]. The kidney is responsible for HGF clearance to a limited extent.

Hepatocyte growth factor receptor

The c-*met* proto-oncogene is known to encode a receptor-like transmembrane protein; 50-kDa α and 145-kDa β subunits are generated by cleavage of a single precursor[49,50]. The β unit has both extracellular and intracellular domains; the latter has tyrosine kinase activity. The discovery of the relationship between HGF and c-*met* was first reported[13,51] in 1991. It was found that HGF could induce tyrosine phosphorylation of p145, the c-*met* proto-oncogene β subunit product. This was supported by affinity cross-linking experiments and subsequent separation of the HGF–c-*met* complex. The HGF receptor on hepatocytes was initially described as having two classes of binding affinity[52] and induces signal transduction via tyrosine phosphorylation[53] and changes in the cytosolic free Ca^{2+} level[54]. It has recently been demonstrated by Weidner *et al.*[55] that tyrosine kinase transduces all the effects of HGF on motility, growth and morphogenesis. Activation of protein kinase C, however, may inhibit c-*met*-mediated activities[56]. A wide range of cells and tissues that have been shown to express the HGF receptor or the c-*met* protein are listed in *Table 2*. Not included in *Table 2* is the receptor status of breast and breast carcinoma tissue because there is a controversy in this regard. Prat *et al.*[57], and Di Renzo and colleagues[58] failed to detect c-*met*/HGF receptor in either Northern or Western blotting analyses, or immunohistochemical studies. In contrast, Tsarfaty *et al.*[65] reported recently that both normal and malignant breast cells and tissues are c-*met*/HGF receptor positive by immunogold staining; furthermore, it was also shown that various breast cancer cells respond to HGF.

Table 3 *Increased circulating hepatocyte growth factor level in liver disease*

Reference	Liver damage	Assay
	Rat	
Asami *et al.*[66]; Lindroos *et al.*[67,68]	Chemical (carbon tetrachloride)	Hepatocyte DNA
Lindroos *et al.*[67]; Zarnegar *et al.*[69]	Hepatectomy	Northern blotting
Kinoshita *et al.*[70]	Hepatotoxins	Northern blotting
	Human	
Gohda *et al.*[71,72]	Hepatic failure	Hepatocyte DNA
Tsubouchi *et al.*[73-75]	Hepatic failure	ELISA
Tomiya *et al.*[76]	Hepatic failure	ELISA
Shimizu *et al.*[77]	Liver cirrhosis	Hepatocyte DNA
Tomiya *et al.*[76]; Tsubouchi *et al.*[78]; Kaneko *et al.*[79]	Chronic liver disease	ELISA
Kaneko *et al.*[79]; Sakon *et al.*[80]	Hepatectomy	ELISA
Kaneko *et al.*[79]	Transcatheter arterial embolization	ELISA
Nagaike *et al.*[81]	Nephrectomy	Northern blotting, hepatocyte DNA

After hepatectomy blood hepatocyte growth factor level could rise as high as 100 (range 10–100) ng/ml. ELISA, enzyme-linked immunosorbent assay

Regulation of liver regeneration by hepatocyte growth factor

HGF is the most potent known stimulus for DNA synthesis by normal hepatocytes, a process that is essential for the proliferation of such cells during liver regeneration. After hepatectomy, and in a variety of liver diseases, there is a marked increase in the level of circulating HGF (up to 100 ng/ml) and increased expression of HGF mRNA in a variety of tissues (*Table 3*). It has been suggested, therefore, that HGF is a key factor for triggering liver regeneration after hepatectomy or other damage to the organ. This suggestion is strengthened by the demonstration that, after injection of labelled HGF into rats subjected to hepatectomy, there was a marked increase of HGF binding to the liver remnant[82]. Furthermore, infusion of HGF accelerated liver regeneration. Similar changes were seen in experiments with chemically induced cirrhotic liver (*Table 3*). Under these conditions, the lung may serve as the major contributor of HGF for liver regeneration[38].

In patients with fulminant hepatitis, very high concentrations of HGF are associated with a poor prognosis. The high levels reflect both the extent of the decrease of functioning hepatocyte mass and also the reduced capacity of liver to remove HGF[75].

Regulation of the regeneration of other organs by hepatocyte growth factor

There is evidence that HGF is also an important factor in kidney regeneration after surgical resection; levels of circulating HGF, mRNA for HGF and HGF receptor (c-*met*) are all increased[39,81,83] after unilateral nephrectomy. These changes may also be mediated by 'injurin'[39].

Hepatocyte growth factor and metastasis

Because of its profound effects on cell growth and motility, HGF may well be important in the growth and development of cancer metastases. Cell motility is a basic requirement for cancer cells to establish distant metastases[84] and the ability of HGF to induce motility in various cancer cells has raised understandable interest.

Overexpression of c-met *hepatocyte growth factor receptor in cancer cells*

It has been clearly shown that normal tissues, including gastrointestinal mucosa, express low or undetectable levels of mRNA for c-*met*, whereas related malignant counterparts express much higher levels of the message[62]. This receptor overexpression in malignant cells is seen in various tissues and in other transformed cells (*Table 2*). Transfection of cells that were initially negative for HGF and its receptor with c-*met* cDNA caused them to become motile and invade through the basement membrane when stimulated with HGF[85]. Transfection with the c-*met* gene also increased the tumorigenicity of malignant cells[86]. This raises the possibility that malignant cells expressing high levels of the HGF receptor are more sensitive and respond more vigorously to HGF, so becoming more motile than non-malignant cells when exposed to the factor.

It has recently been discovered that cancer cells have defective post-translational processing of the c-*met* protein. As described above, production of this protein involves synthesis of a 190-kDa precursor with subsequent cleavage to the α and β subunits that form the mature HGF receptor[54]. Activation of the mature receptor requires binding of HGF. However, in some cancer cells there is a defect in the cleavage process and the 190-kDa precursor appears in the plasma membrane. Since the precursor is itself active without ligand binding, these cells lose the control exerted by HGF and have increased motility in the absence of exogenous HGF[87].

Overexpression of the HGF receptor on malignant cells is clearly distinct from that on normal cells. Although after organ (liver or kidney) resection there is a temporary increase in HGF receptor expression on normal cells (e.g. hepatocytes), the level of expression returns to normal soon after the insult[53,88,89]. The exact underlying mechanism is not clear but this phenomenon provides evidence that normal cells and organs have the ability to control their response to HGF by reducing receptor expression, whereas malignant cells consistently overexpress the receptor and so may over-react to HGF. This may contribute to the motile and invasive nature of malignant cells.

Paracrine and autocrine regulation by hepatocyte growth factor

Levels of HGF increase in blood and other biological fluids in a number of conditions apart from liver damage. It has been shown that blood levels of HGF increase after liver resection of metastatic tumours[80]. Kaneko *et al.*[79] showed, in patients with liver metastases who had higher levels of circulating HGF than normal controls, that these levels were raised further after resection of metastatic foci in the liver. Even routine surgical operations such as cholecystectomy, colectomy and splenectomy may induce significant increases in blood HGF levels[90]. It has also been reported that patients with cancer metastases in the lung and pleura have high HGF levels in the pleural exudate[91].

Tumour cells may also produce HGF themselves; HGF or mRNA encoding this factor has been detected in fibrosarcoma[34], lung cancer[41,64,92], hepatoma[93] and pancreatic cancer[94] cells. Taken together with the high level of expression of HGF receptors on lung cancer cells[14,41,64], there exists the possibility of autocrine regulation of cancer cell motility. This is strongly supported by recent work by Rong *et al.*[86]: when cells that produced large amounts of HGF were transfected with the c-*met*/HGF receptor gene they became tumorigenic.

Angiogenesis induced by hepatocyte growth factor

The other important aspect of cancer growth and metastasis is the establishment of neovasculature by angiogenesis[95]. By inducing endothelial cell proliferation and motility, HGF can stimulate neovascularization *in vivo*[22,96,97]. This suggests that HGF, apart from increasing the invasiveness of cancer cells, may also stimulate primary and secondary tumour growth by modulating the tumour matrix. Thus, cancer cells expressing HGF receptors will become invasive and may form distant metastatic foci when exposed to HGF generated as a result of certain insults such as liver or kidney resection, or even excision of the tumour itself. In addition to this paracrine effect, autocrine production of HGF by tumour cells may also act as a positive feedback to reinforce the process.

Although HGF may be the key factor regulating tumour invasiveness, other motility agents exist, such as autocrine motility factor[98], migration-stimulating factor[99], tumour necrosis factor α[100], epidermal growth factor[101], IL-6[102], TGF-β[103], interferon γ[104], platelet-derived growth factor[105] and monocyte-derived scattering factor[106]. The regulatory mechanisms for these factors, the expression of their receptors and the interplay between them has yet to be elucidated.

The future of hepatocyte growth factor in clinical treatment

Two possible interventions aimed at reducing HGF-induced metastasis can be suggested, one aimed at lowering the responsiveness of cancer cells to HGF and the other at reducing HGF production. It has been shown that TGF-β and glucocorticoid reduce the level of mRNA for HGF[36,41] and HGF secretion[45]. Somatostatin inhibits HGF-induced growth of hepatocytes[107] but its effect on HGF-induced motility has yet to be established. An antagonist of HGF has recently been reported[108] that may compete with receptors for HGF binding without inducing adverse biological effects. Reduction of cell motility using a c-*myc* antisense oligonucleotide[109], cancer cell motility-inhibitory protein[110], extracellular matrix protein Arg–Gly–Asp sequence[111], tumour invasion-inhibiting factors[112] and other synthetic peptides[113] are other possible lines of approach for the future.

In conclusion, HGF is a factor that regulates growth, motility and morphogenesis. It plays key roles in the regeneration of liver and other organs and also in cancer metastasis. A further understanding of its role will have implications for clinical practice.

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Review

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'Bile' in the oesophagus

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Acid gastro-oesophageal reflux occurs when the lower oesophageal sphincter is incompetent, but oesophagitis caused by reflux of duodenal content implies incompetence of both the pyloric and gastro-oesophageal sphincters. The term 'alkaline' reflux oesophagitis was coined long before objective analysis was made of bile in the stomach and oesophagus, and well before pH monitoring was introduced. Surgical procedures to divert bile from the stomach and oesophagus were developed on a clinical basis and gave encouraging results in the management of peptic oesophageal stricture. Alkaline oesophagitis is well recognized after gastric surgery and the entity 'primary pathological duodenogastric reflux', although contested by some, attracts growing support. Recent evidence suggests that the complications of Barrett's oesophagus may be related to duodenogastro-oesophageal reflux. Probes designed to measure gastric and oesophageal bile salts have recently been developed and may give more information in the future.

Gastro-oesophageal reflux disease (GORD) has become a common condition in most Westernized societies. The role that gastric acid plays in its pathogenesis is well established[1] and forms the basis for medical therapy. Many patients, however, fail to respond to potent acid-suppressing drugs such as omeprazole. This drug heals oesophagitis in 67–92 per cent of patients overall and, although successful for the lower grades of oesophagitis, will heal only 48–62 per cent of those with grade IV disease[2]. The reason why such marked acid suppression fails to heal all cases needs to be explained; one possible reason for failure is that the reflux contains duodenal contents that are not suppressed by omeprazole. Furthermore, oesophagitis is seen in patients with atrophic gastritis, pernicious anaemia and following total gastrectomy[3–5], indicating that the pathology may also be caused by 'acid-free' reflux. These facts led to the concept of 'alkaline' reflux oesophagitis which, although debated for decades, is still not completely understood or even accepted. Alkaline flushes (pH > 7) demonstrated in the oesophagus by ambulatory pH monitoring may indicate exposure to duodenal contents, namely bile and pancreatic juice, both of which potentially cause mucosal damage. Pellegrini *et al.*[6] measured pH values >7 in the oesophagus and recognized three kinds of abnormal gastro-oesophageal reflux: acid, mixed acid–alkaline and alkaline. Alkaline gastritis, a better accepted entity than alkaline oesophagitis, is a common complication after gastric surgery. Blum *et al.*[7] questioned the relevance of primary duodenogastric reflux, and considered alkaline gastro-oesophageal reflux to be an uncommon condition. Gowen[8], however, identified 42 patients who met the criteria for primary enterogastric reflux gastritis and oesophagitis. All had a constant burning epigastric pain that was worse after meals and unrelieved by antacids or diet, endoscopic evidence of a gastric bile pool, endoscopic biopsy proof of gastritis and oesophagitis, and hypochlorhydria.

Crumplin *et al.*[9] also showed that there was an increase in total bile salts in the gastric aspirate from patients with sliding hiatal hernia and reflux stricture. Using these same criteria in another study, ten patients with primary pyloric incompetence and complicated alkaline oesophagitis were treated by vagotomy and Roux-en-Y diversion with good results[10].

Pathophysiology of oesophageal mucosal damage

In 1833, Beaumont reported observations on his patient Alexis St Martin and noted that 'bile was seldom found in the stomach except under special circumstances'[11]. Du Plessis[12] in 1965 and Capper[13] in 1967 presented evidence suggesting that duodenogastric reflux played a role in the pathogenesis of gastric ulcer and gastritis. Teorell[14] reported on the effect that bile had on the permeability of the gastric mucosa to hydrogen ions (H^+), and Davenport[15] showed that bile could break down the gastric mucosal barrier. Lillemoe *et al.*[16] demonstrated that, in the normal state, a mucosal barrier exists in the oesophagus in much the same way as had been shown previously in the stomach. Furthermore, it was shown in a rabbit model that bile was actually absorbed during disruption of this oesophageal mucosal barrier and that the net flux of H^+ through the rabbit oesophageal wall increased with increasing concentrations of taurodeoxycholate[16,17]. Oesophageal mucosal resistance, which prevents injury from noxious substances, has several components. Oesophageal motility and salivary flow assist with oesophageal clearance[18], while mucosal tight junctions, intercellular matrix and endogenous leukotrienes act as diffusion barriers[19]. The cellular contribution to protection comprises resistant cell membranes, cytoplasmic proteins, bicarbonate transport mechanisms and Na^+–H^+ exchange mechanisms to maintain intraoesophageal pH[19]. In the experimental rabbit model, luminal acid does damage the oesophageal mucosa, but high concentrations (300 mmol/l HCl) are needed to exert even minor influences on mucosal integrity[20]. The addition of taurocholate, pepsin and lysolecithin, however, causes severe mucosal damage even with lower rates of H^+ diffusion[17]. Erosive oesophagitis can be produced in dog models with bile, pancreatic juice or a mixture of the two[21–23]. These observations led to laboratory confirmation of the deleterious effect of bile on the oesophageal mucosa of monkeys. Gillison *et al.*[24] showed that acid reflux alone rarely caused oesophagitis, but a mixture of bile and acid produced serious oesophagitis and stricture formation. More recently, Safaie-Shirazi *et al.*[25] showed that H^+ flux through the oesophageal wall was minimal with acid reflux but increased fivefold when bile acids were added to the reflux in dogs and humans.

Measurements in humans

Whether bile acids or pancreatic juice play a causative role in the development of oesophagitis in the human is controversial[23]. Most of the evidence supporting oesophageal mucosal injury by bile came from animal experiments. But do duodenal contents, be they bile, pancreatic juice or a mixture,

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cause oesophagitis in humans? Following total gastrectomy and oesophagojejunal anastomosis, severe oesophagitis results clinically and in the experimental model[3]. Bile diversion affer total gastrectomy with Roux-en-Y reconstruction prevents oesophagitis and is currently a standard technique. Bile diversion procedures were used clinically to treat severe oesophagitis and stricture formation long before experimental studies investigated the role of bile in the pathogenesis of oesophagitis. Good results after these operations without prior laboratory proof of alkaline reflux were reported by independent investigators[26,27].

The presence of bile in the oesophagus of patients with oesophagitis but with an intact stomach and pylorus is not well documented. A role for bile in the pathogenesis of oesophagitis seemed probable when Gillison *et al.*[28] reported duodenogastric reflux in 52 of 59 patients with heartburn and in only four of 21 controls. Kay and Showalter[29] also found increased bile concentrations in the stomach of about half of patients with peptic oesophagitis and peptic oesophageal stricture. Increased concentrations of bile have also been detected in the gastric aspirate of patients with oesophagitis[30].

Duodenogastric reflux and complicated Barrett's oesophagus

In 1977, Bremner[31] postulated that bile reflux was involved in the pathogenesis of Barrett's ulceration, and in 1981 Bremner and Hamilton[32] reported increased levels of bile acids in the gastric juice of some patients with Barrett's oesophagus. The columnar lining of the oesophagus develops in the presence of severe acid gastro-oesophageal reflux and it was suggested that acid reflux alone was unlikely to cause ulceration or stricture formation. In 1985, Bremner and Hamilton[33] reported an increased gastric bile acid content in patients with Barrett's stricture. In 1988, Gillen *et al.*[34] showed that postprandial gastric bile acid concentrations were significantly greater in patients with complications associated with Barrett's oesophagus than in those with uncomplicated disease, giving support to Bremner's hypothesis. Using hepatobiliary scanning techniques, Waring *et al.*[35] demonstrated duodenogastric reflux in six of 13 patients with Barrett's oesophagus and in only two of 19 controls. Attwood *et al.*[36] in 1989 again showed a strong relationship between the presence of duodenogastric reflux and the occurrence of complications associated with Barrett's oesophagus. All of these experiments provided indirect evidence implicating bile or duodenal contents in the pathogenesis of the complications of Barrett's oesophagus.

Bile salts in the oesophagus

The demonstration of increased levels of bile salts in the stomachs of patients with symptomatic gastro-oesophageal reflux strongly suggests that bile refluxes into the oesophagus of these patients. Gotley *et al.*[30] performed continuous aspiration of the oesophagus in control subjects and patients with oesophagitis; conjugated bile acids were detected in the oesophagus of most patients with oesophagitis and this reflux occurred mostly during supine resting periods. Johnsson *et al.*[37] also sampled oesophageal contents during ambulatory 24-h pH monitoring in 18 patients with oesophagitis; all but one had bile salts in the oesophagus. The concentration of bile salts was low, however, and similar to that found in the gastric juice of the ten normal controls. In similar aspiration studies performed by Mittal *et al.*[38] only small amounts of bile were detected in the oesophagus. Duodenal contents detected in the oesophagus in small concentrations may be of no consequence at all; Gotley *et al.*[39] found bile in sufficient concentrations to cause mucosal damage in only 2 per cent of oesophageal aspirates in patients with GORD. Gotley *et al.*[30] also pointed out the fallacies of using the 3α-hydroxysteroid dehydrogenase enzymatic technique for analysis of bile acids; they used a sensitive and specific liquid chromatography method to assay six of the most prevalent bile acid conjugates. An important finding of their study is that gastric juice containing potentially cytotoxic levels of bile acids frequently has a pH $<3{\cdot}5$, which would be registered as acid reflux. Very recently, Stein *et al.*[40] used the new technique of combined ambulatory oesophageal aspiration and pH monitoring to demonstrate an increase in the presence of bile acids in the oesophagus of patients with erosive oesophagitis and Barrett's oesophagus. Interestingly, this increase was again shown to be maximal during supine periods, and there was a significant correlation between bile acid concentration in the aspirate and the proportion of time that a pH >7 was observed on the ambulatory oesophageal pH monitor. Trypsin was seldom found in the aspirates studied by Gotley *et al.*[41], but pepsin concentration was high in patients with stricture and Barrett's oesophagus; it was concluded that pepsin in an acid medium may be responsible for the oesophageal damage.

Bremner *et al.*[42] also showed that the greatest prevalence of mucosal damage to the oesophagus occurred in patients with increased oesophageal exposure to a pH of 0–2, corresponding to the known pK_a of pepsin, and in those with an increased exposure in the pH 7–8 range. Pepsin, therefore, causes mucosal damage in an acid environment and trypsin is destructive at pH 5–8. Alkalinization of the stomach by effective antacid therapy in patients with gastro-oesophageal reflux could theoretically be harmful by allowing reflux of trypsin in an alkaline environment.

Duodenogastric reflux and cancer

Yasui *et al.*[43] recently compared results of 24-h gastric and oesophageal pH monitoring in 17 patients with early gastric cancer and 42 with Barrett's oesophagus; it was found that in complicated Barrett's disease and early gastric cancer pathological duodenogastric reflux was present. Such reflux was, however, inferred from recordings of pH$>$7.

Bile is known to be associated with gastrointestinal carcinogenesis, an effect that is not confined to the stomach or oesophagus. Nagengast[44] presented evidence to suggest that bile promotes carcinogenesis in the colon. As has already been discussed, there is strong evidence that ulceration and stricture formation in Barrett's oesophagus may be related to alkaline reflux oesophagitis. Is it possible that the same irritants from duodenogastric reflux are associated with the development of adenocarcinoma in the columnar-lined oesophagus? There is experimental evidence in the rat model to show that adenocarcinoma may develop in the presence of duodeno-oesophageal reflux[45,46].

Improved techniques are being used to detect duodenogastric reflux. Ambulatory gastric pH monitoring has shown an increasing prevalence of such reflux in symptomatic patients that was not seen with isotope scanning techniques using di-isopropyl iminodiacetic acid[47]. Using discriminate analysis, a composite scoring system with 16 variables of circadian gastric pH recording was shown to differentiate patients with known duodenogastric reflux disease from normal volunteers[48]. Recording pH, however, is an indirect measurement that assumes duodenogastric reflux.

The future

An intraoesophageal probe that can continuously measure ^{99m}Tc-labelled bile reflux into the stomach or oesophagus has been developed. The technique is, however, qualitative and will not measure concentration[49]. More recently, Bechi *et al.*[50] reported use of a fibreoptic sensor for ambulatory assessment of enterogastric and non-acid gastro-oesophageal reflux. The basic working principle in this apparatus is that an absorption peak centred around 453 nm in the gastric or oesophageal lumen automatically implies the presence of bile reflux. If this apparatus proves to be a reliable tool for measuring bile in the gastrointestinal tract, the mysteries of alkaline reflux oesophagitis could be resolved.

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Association of Surgeons of Great Britain and Ireland

A meeting of the Association of Surgeons of Great Britain and Ireland took place in Birmingham on 14–16 April 1993. The President of the Association, Miss Averil O. Mansfield, was in the chair.

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Organization of general surgical services in Britain: strategic planning of workload and manpower

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At the 1993 annual general meeting of the Association of Surgeons of Great Britain and Ireland there was a vigorous debate on the number of consultants required to meet the future needs of general surgery. This deliberation continued the discussions of previous meetings in which detailed studies of surgical workload were reported[1]. That workload related to the provision of acute services and it was recognized that acute hospitals must be large enough to provide a comprehensive range of specialist skills[2]. There is already evidence from the Department of Health circular *Achieving a Balance*[3] that consultant numbers in the UK need to be increased. Analysis of service load, the number of acute sites and the need for concentration of specialist skills suggests that a new initiative is urgently required to increase markedly the number of consultant general surgeons in Britain.

At this year's meeting Mr Peter Doyle, a senior registrar in public health medicine, spoke on existing surgical manpower resources and the effects of the 'new deal'[4] on junior doctors' hours. The new training responsibilities for consultants and the new role of postgraduate deans were reported by Mr John Temple, speaking as a surgeon and postgraduate dean[5]. Mr Robert Baigrie of the Association of Surgeons in Training also described the problems faced by surgical trainees and how they might be solved within the constraints of the new deal.

Peter Doyle's analysis of general surgical manpower using the latest Department of Health Medical Manpower Census figures from 1991 shows that at the start of this decade there were approximately 1000 consultant general surgeons covering over 300 acute service sites in England and Wales. These general surgeons serve a population of more than 50 million, giving a ratio[6] of approximately 1:50000. They include specialists in vascular surgery, renal transplantation and other subspecialties, most of whom have continued involvement in providing emergency general surgical cover. Subspecialty cover is even more thinly spread: for example, in vascular surgery there is only one consultant for every 211000 individuals[7].

There has been a gradual but slow increase in consultant numbers in recent years: at best 3 per cent and at worst 1 per cent per year. If the best rate of expansion is maintained, there will be 1408 general surgical consultants by the year 2000, but only 1180 if expansion is at a rate of 1 per cent. Even 3 per cent would fall short of the target identified by the Association to supply one general surgeon for every 30000 population; this ratio is presently achieved only in Northern Ireland and parts of Scotland. The population of England and Wales is projected to reach 53 million by the year 2000. It would then require more than 1700 general surgeons to reach the target, an increase of 66 per cent over current levels. Such an expansion would bring Britain more closely into line with several other European countries.

The current trends are inadequate to meet the requirements of the new deal on junior doctors' hours or the challenges of modern postgraduate training. The new deal for junior hospital doctors has established a maximum emergency commitment of 1 in 5 as desirable if a 1 in 4 service with internal cover is to be applied to all grades of staff. This must be so if high standards are to be preserved. Three levels of competence are required for a modern emergency service in a hard-pressed specialty[8]: house surgeon, intermediate grade and consultant. The intermediate-grade doctor may be a registrar, senior registrar or an experienced senior house officer who is defined by the national safety-net agreement[3] as one who has spent a minimum of 1 year after registration in surgery in general. Consultants who are not recognized as trainers would need the support of a career-grade person such as a staff-grade doctor. Assuming a 1 in 5 rota and taking account of the requirements of the central Joint Planning Advisory Committee and the reduced length of training, the present intermediate-grade surgical manpower in the UK could cover only 165 acute sites, that is just over half those currently providing acute services. These are powerful additional forces to promote the merging of adjacent units and the end of split-site working.

John Temple also pointed out that the reduced hours of the new deal will lead to an increase in the workload for both trainees and consultants, and it will be vital to provide protected time for education during normal working hours. There will be fewer trainees, and not all consultants will be trainers. Standards of training will be defined and required by contracts, and time will be needed for formative assessment and for certification of the competence of trainees. Shorter structured training and the need for continuing medical education (continuing professional development) will demand more consultant time. That demand will be met only by an expansion in the number of consultants. Such expansion is fully supported by the Association of Surgeons in Training, whose members remain overexperienced and undertrained. Junior staff saw expansion in consultant numbers as essential; they gave no support to the concept of service provision by a doctor of subconsultant grade.

There are also the issues of specialist registration in the European Community. The suggestion has been made that all experienced registrars and senior registrars should receive independent specialist status to achieve harmonization within Europe, but even this development would hardly approach the desired ratio. It would also be likely to degrade the high standards of consultant practice in the UK. Shorter structured training could, however, make a useful contribution to consultant manpower by accelerating the addition of fully trained surgeons to the permanent workforce. Such a solution would reduce the trainees' contribution to the service at the intermediate grade and make the rationalization of services and acute sites even more necessary.

Since the meeting of the Association, Council has considered and responded to the Calman Report[9], pointing out that these

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new proposals will also demand more consultants. The Association believes that the Calman objectives can be achieved only by sustained political determination and substantial new money. All these issues – manpower planning, postgraduate training, hours of work and the distribution of specialist services – have come together to support the *ten principles* developed and agreed by the Association. These principles concern strategic planning of workload and manpower in general surgery, excluding urology:

1. The Association is committed to improving the quality of patient care by moving towards a consultant-based service before the year 2000. This objective can be achieved only through a substantial increase in the number of consultant surgeons.
2. The Association reaffirms the principle that all surgical patients should remain the responsibility of a named consultant duly appointed by a properly constituted advisory appointments committee. Only consultants should be responsible for appropriate delegation of work to more junior staff.
3. A general surgeon is defined as one who participates in the emergency rota for general surgery in addition to his or her subspecialty interest.
4. The Association confirms that the desirable ratio of consultant general surgeons to catchment population is 1:30 000 (current mean 1:50 000)[6]. Such a ratio would lead to an improvement in the quality of care for patients undergoing emergency, urgent and elective procedures. It would also facilitate the training of junior doctors.
5. The Association fully supports recommendations by the National Confidential Enquiry into Peri-Operative Deaths that emergency surgery should be carried out during the day whenever possible, that this requires the provision of appropriate facilities and that, when the surgeon is 'on take' for emergencies, he or she should have no other responsibilities likely to delay treatment of patients.
6. The Association recommends that the job plan of a full-time or maximum part-time consultant in general surgery in the National Health Service should include one or two outpatient sessions (1–2 notional half-days), of which some may take place outside base hospitals, and three or four operating sessions (3–4 notional half-days) per week[10]. These sessions should be supported by an adequate number of beds and other facilities, bearing in mind emergencies, the consultant's special interest and the age structure of the population.
7. Service contracts based on intermediate (or hernia) equivalents should be sensitive to case mix and the needs of trainees[1]. An appreciable proportion of a consultant's operating time will be spent on the training of junior staff, which will become more structured and intensive. Employing authorities must recognize and budget for this crucial activity. Individual service contracts should take account of the importance of funded study leave in continuing medical education (continuing professional development) and allow for annual and professional leave.
8. A consultant rota commitment for emergency admissions in general surgery should not normally exceed a mean of 1 in 5. Onerous emergency commitments may be recognized by appropriate time off.
9. The Association regards continuing education by and for consultants as mandatory and supports its inclusion as a contractual obligation. At least 1 notional half-day session per week is required for continuing education.
10. The Association believes that the provision of efficient general surgery requires the concentration of acute services on one site serving a population[2] of approximately 300 000. This figure may have to be modified in areas with a widely dispersed population. The ideal acute hospital requires: (1) ten general surgeons with appropriate subspecialty interests and adequate junior staff support to facilitate cover; (2) an intensive care unit with sufficient beds and trained staff; and (3) facilities for the prompt treatment of surgical emergencies, with theatres and support services available on a 24-h basis and access to other specialist services.

These ten principles have been extensively discussed and refined by the Association and approved at the annual general meeting. They provide a clear direction for the development of general surgical services for this decade and the next generation.

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Eye protection for the vascular surgeon

Contamination occurring during vascular surgery was studied prospectively using a surgical mask incorporating a Splashguard visor. Over a 16-week period 78 vascular procedures were included; 44 were of <2 h duration and 34 were of $\geqslant 2$ h. Contamination on both mask and visor from blood spots was recorded at the end of each procedure. Overall, 51 per cent of principal surgeons' visors were contaminated, with contamination of the mask itself in 32 per cent. When two surgeons were operating the contamination rate for the second was also high: 36 per cent for the visor and 42 per cent for the mask. Assistants had a contamination rate of 36 per cent for the visor and 13 per cent for the mask. The lowest rate of contamination occurred for the visor and mask of the scrub nurse, 10 and 4 per cent respectively. For emergency procedures the duration of operation had no influence on the frequency of contamination. However, for the principal surgeon elective operations of <2 h duration were less likely to involve contamination than those of $\geqslant 2$ h ($\mathrm{P}<0{\cdot}035$). Blood contamination of visors and masks is common in vascular surgery but rarely appreciated by the surgeon. Routine eye protection should be considered in vascular surgery, in particular for emergency and prolonged elective procedures.

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Vascular surgeons are inevitably at risk[1] from hepatitis B and human immunodeficiency virus (HIV). Although for high-risk patients full precautions are advisable[2], the level of protection that should be used for other patients is less clear. Double gloving reduces the number of glove punctures[3] and probably should be used in all major thoracic, abdominal and femoropopliteal reconstructions. For femorotibial or femoroperoneal reconstruction double gloving may impair the fine touch necessary for dealing with these smaller vessels.

Eye protection for orthopaedic[4,5], otorhinolaryngology[6] and maxillofacial[7] surgeons has recently been advocated, particularly when power tools are in use. However, scant regard has been paid to the potential conjunctival route of transmission in vascular surgery. Brealey and Buist[8] studied a consecutive series of 257 operations of which 25 were arterial in nature. Visors or protective glasses were not worn but the number of spots contaminating ordinary spectacles was noted. Of the 25 arterial procedures, 11 caused contamination of spectacles, but no reference was made to the type of arterial operation performed, or to the contamination of the assistant or scrub nurse. Furthermore, these authors stated that 'conventional spectacles provide only partial protection: several of the blood splashes were on the inner surfaces of our lenses.' The present study examined the contamination occurring during major vascular surgery, using a surgical mask incorporating a Splashguard visor (Universal Hospital Supplies, London, UK).

Patients and methods

For 78 consecutive vascular operations performed over a 16-week period, the surgeon(s), first assistant and scrub nurse were requested to wear a Splashguard visor mask throughout the entire procedure. At the end of the operation the mask and clear plastic visor were graded separately for macroscopic contamination with blood splashes. The total number of separate splashes was counted and any major contamination recorded. A record was also kept of elective and emergency cases, the nature of the operation performed and its duration. Results are expressed as mean(s.d.) or median (range) as appropriate. Statistical analysis was performed using the χ^2 test.

Results

Seventy-eight consecutive vascular procedures (50 elective, 28 emergency) performed over a 16-week period were studied. Forty-four procedures were of <2 h duration, mean(s.d.) 76(34) min, and 34 were of $\geqslant 2$ h, mean(s.d.) 188(61) min. Procedures ranged from ruptured aortic aneurysm repair to amputation and vein surgery (*Table 1*).

Contamination with blood spots on both mask and visor, as recorded at the end of each procedure, varied considerably according to the role of the wearer. Of principal surgeons' visors 51 per cent were contaminated (median number of spots 6 (range 1–35)), with contamination of the mask itself in 32 per cent (median number 4 (range 1–40)). For a second operating surgeon the contamination rate was also high, 36 and 42 per cent respectively. Contamination rates decreased with increasing distance from the site of surgery. The contamination rate for the assistant was 36 per cent for the visor but only 13 per cent

Table 1 *Procedures performed*

	Elective	Emergency
Carotid endarterectomy	1	0
Abdominal aortic aneurysm repair	9	6
Axillobifemoral graft insertion	2	2
Femoral false aneurysm repair	2	2
Profundoplasty	2	0
Femoropopliteal or femorodistal bypass	12	3
Iliofemoral crossover bypass	1	1
Iliopopliteal bypass	2	0
Iliac–superior mesenteric artery bypass	1	0
Femoral embolectomy	1	8
Femoral artery or vein repair	0	2
Infected aortobifemoral graft excision	0	1
Supraclavicular neck dissection	1	0
Exploration of artery	2	1
Varicose vein surgery	8	0
Above- or below-knee amputation	3	0
Other	3	2
Total	50	28

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Table 2 *Contamination of visors and masks*

	Visor		Mask	
	Contaminated (%)	Median (range) no. of splashes	Contaminated (%)	Median (range) no. of splashes
Principal surgeon	51	6 (1–35)	32	4 (1–40)
Second surgeon	36	3 (2–34)	42	1 (1–6)
Assistant	36	3 (1–12)	13	3 (1–3)
Scrub nurse	10	2 (1–4)	4	2 (1–3)

for the mask. The scrub nurse showed the lowest rate of contamination, blood affecting the visor in 10 per cent of cases and the mask in 4 per cent (*Table 2*).

There were three instances of major contamination; in all cases a power saw was in use for bone division as part of amputation. With the exception of these three cases, most contamination was not noticed by the surgeon during the course of the procedure.

For emergency cases the duration of the operation had no influence on the frequency of contamination. However, for the principal surgeon elective operations of <2 h duration were less likely to involve contamination than those of $\geqslant 2$ h (34 *versus* 65 per cent, $P<0.035$).

Discussion

Although the risk to healthcare personnel of contracting hepatitis B has been recognized for many years, surgeons have been slow in adopting preventive measures in surgical practice. The availability of hepatitis B immunization has reduced the risk of infection but, despite this, uptake of immunization among vascular surgeons is not universal[1]. Increased awareness of the risk of HIV infection, however, has accelerated progress in the protection of theatre personnel in general. Extra precautions can obviously be adopted for at-risk cases – patients with known infection or those belonging to high-risk groups. However, there will always be patients who, possibly unknown to themselves, carry the HIV and/or hepatitis B virus. Also, for patients who test negative for HIV infection, it has been suggested that seroconversion can be prolonged, possibly as late[9] as 36 months.

Some surgeons may feel that their normal spectacles offer sufficient protection but contamination may occur on the inner aspect of the lenses[8]. Furthermore, Bell and Clement[5] demonstrated a 5 per cent rate of contamination of protective side flaps. Conjunctival transmission of hepatitis B can occur and HIV may also be transmitted via this route. While Seale[10] has suggested that it may require only one viral particle of HIV to allow transmission, making blood splashes to the conjunctiva a real problem[11,12], the actual risk is small. In a survey of 938 healthcare workers known to have incurred parenteral or mucous membrane exposure to blood or other body fluid from patients with acquired immune deficiency syndrome or related illnesses, only two were found to be seropositive. One had been contaminated with a colonic biopsy needle and the other by a deep, hollow needlestick injury[13]. As far as the present study is concerned, it must also be recognized that the surface area of the conjunctiva is much less than that of the visor; contamination of the latter does not necessarily equate with eye contamination.

This study has demonstrated that blood contamination of visors and masks is common during vascular surgery. Blood splashes occur particularly in emergencies and in elective procedures lasting 2 h or more. Although the risk of serious infection currently appears to be small, over a surgical career the cumulative risk may be significant. The authors suggest that eye protection should be seriously considered for all types of vascular surgery but, in particular, for emergencies and prolonged elective operations.

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Genetic linkage analysis applied to unaffected women from families with breast cancer can discriminate high- from low-risk individuals

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Up to 20 per cent of cases of breast cancer diagnosed in women under the age of 45 years may be caused by an autosomal dominant gene. A present difficulty is differentiation of mutation carriers from non-mutation carriers in high-risk families. Genetic linkage analysis has been used to localize a susceptibility gene (BRCA1) *on chromosome 17q12-21 between markers 42D6 and MFD188, a region 5–10 million base pairs in length. Odds in favour of linkage to this region were greater than 100 000:1 in 15 families with breast cancer. In eight families in which the probability of linkage was above 75* (*range 79·2–99·9*) *per cent, 19 women were identified who were at high lifetime risk of breast cancer* (*range 80·6–87·2 per cent*) *and 37 whose risk was similar to that for the general population* (*range 9·8–16·4 per cent*). *Genetic risk prediction of this kind may enable high-risk screening clinic resources to be concentrated on those most likely to benefit.*

A major risk factor for breast cancer is a positive family history of breast malignancy, especially when affected relatives have included those of young age with bilateral disease[1–6]. A common feature of heritable breast cancer is the occurrence of families in which malignancy is diagnosed early in life, although in these the disease is not always distributed according to strict mendelian principles. Genetic epidemiological studies (segregation analysis), however, consistently suggest that these pedigrees do not simply represent chance clusters of cancer. They frequently reflect the phenotypic effect of single autosomal dominant genes that are carried in 1–6 of every 1000 individuals and which give a greater than 80 per cent lifetime risk of breast cancer with a 40 per cent risk before the age of 50 years[7–9].

These epidemiological features of familial breast cancer suggest that, in the catchment area of the Edinburgh Breast Unit (population of south-east Scotland approximately 1 million), 750 women between 30 and 50 years of age will be carriers of a major breast cancer susceptibility gene. Approximately 15 breast cancers per annum would occur in this high-risk group, which corresponds to nearly 20 per cent of the total diagnoses in women between the ages of 30 and 50 years (*Table 1*)[9]. Such a cohort of young women might be a cost-effective group for breast screening with the aim of detecting malignancy early and thereby reducing morbidity and mortality rates from breast cancer. Screening on the basis of family history alone would fail to target many gene carriers since some would be unaware of their family history and others would have inherited the gene through the paternal line or through female ancestors who did not express the disease phenotype. Still others might exhibit *de novo* germ line mutation. Some individuals would have a strong family history of breast cancer simply by chance and without genetic susceptibility. This phenomenon was recognized by Paget[10] over 100 years ago. Furthermore, according to mendelian laws of inheritance, half of the daughters of a mutation-carrying parent would not have inherited the trait and would be at no greater risk than the population as a whole.

It therefore appears unlikely that selection of patients for high-risk clinics based simply on a positive family history would identify susceptible individuals with great specificity or sensitivity. The sites of mutations responsible for familial breast cancer need to be determined and then women who carry them identified. Recent work has centred on the tumour suppressor gene *BRCA1*.

BRCA1 is located[11–13] on chromosome 17q12-21. Genetic linkage analysis, using polymorphic markers in this region to type more than 200 families, has determined that the odds in favour of a breast cancer susceptibility gene existing in close proximity to these markers are many millions to one[14]. This consortium analysis has calculated that *BRCA1* gene mutation is likely to be implicated in the aetiology of malignancy in approximately 50 per cent of families with breast cancer.

In Edinburgh, a total of 206 individuals in 15 families containing between three and nine patients with breast cancer were typed at markers 42D6 and MFD188. Typing was achieved by means of polymerase chain reaction amplification of polymorphic fragments and acrylamide gel electrophoresis. A maximal lod score of +5·62 was obtained on the basis of hypothetical *BRCA1* gene location (θ) 2·5 cM from marker 42D6. The odds in favour of a gene existing at this site were greater than 100 000:1. Recombination data in *BRCA1*-linked pedigrees suggested that 42D6 and MFD188 were probable flanking markers, locating *BRCA1* to a region 5–10 million base pairs in length[15].

Table 1 *Contribution of a major heritable breast cancer gene to breast cancer in general in women aged 30–50 years in south-east Scotland*

	Gene carriers	Non-gene carriers
No. of individuals	750	125 000
Disease penetrance (% per annum)	2	0·05
No. of breast cancers per annum	15	70
Percentage of breast cancers	20	80
Screening viability	Yes	No

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Knowledge of prior probability of *BRCA1* linkage[14] and calculation of lod scores in each family[15] might enable the lifetime risk of breast cancer to be reassessed in female relatives as yet unaffected by the disease. This would be the first step in the process of identification of probable gene carriers, a cohort that might benefit from regular breast screening at an earlier age.

Patients and methods

Fifteen Edinburgh pedigrees each containing at least three patients with breast cancer in blood lineage had been previously typed[15] at markers 42D6 and MFD188. Dates of birth and death and cause of death were confirmed from the records of the Registrar General of Scotland. Where possible, malignant diagnosis was confirmed from hospital sources. Lod scores at 42D6 and MFD188 were calculated for each pedigree on the basis of a genetic model for familial breast cancer produced from a large British epidemiological study[9]. From maximal lod scores, conditional probability of linkage to *BRCA1* was determined for each family according to the equation:

$$x = \frac{100y}{y+1}$$

where x is the percentage conditional probability of linkage and y the inverse $\log_{10}$ maximal lod score. Heterogeneity analysis of lod scores in 214 breast cancer pedigrees (157 site-specific breast cancer families, 57 breast–ovarian cancer subtype families) suggested[14] that up to 50 per cent of site-specific breast cancer families and more than 75 per cent of breast–ovarian cancer subtype families are likely to be linked to *BRCA1*. These values are prior probabilities of linkage to *BRCA1* and are not prejudiced by marker data in any single pedigree.

Bayesian principles of genetics combine prior and conditional probability to calculate final (or posterior) probability[16] according to the equation:

Posterior probability in favour
= (prior probability in favour × conditional probability in favour)
÷ [(prior probability in favour × conditional probability in favour)
+ (prior probability against × conditional probability against)]

Posterior probability in favour of linkage to *BRCA1* was calculated in the 15 families with breast cancer subjected to linkage analysis with *BRCA1* flanking markers. Ten pedigrees were site-specific breast cancer families and five were of the breast–ovarian cancer subtype (which required at least one patient with ovarian cancer in the lineage for classification).

In a single hypothetical pedigree, posterior probability of linkage of 75 per cent indicates that the probability that a mutant susceptibility gene close to the markers that flank *BRCA1* has caused disease in the family is three times more likely than not. Arbitrarily in this study, pedigrees with posterior probability of linkage greater than 75 per cent were considered as probably linked to *BRCA1*. The probability that unaffected women in these 'probably linked' families were carriers of the *BRCA1* mutation was calculated on the basis of *BRCA1* flanking marker data. The lifetime risk of breast cancer in these women was estimated according to the probable presence or absence of *BRCA1* mutation.

Table 2 *Maximal lod score at 42D6 or MFD188 markers, and conditional and posterior probabilities of linkage in eight families with breast cancer with probable* BRCA1 *linkage*

Family	Maximal lod score at marker	Conditional probability of linkage (%)	Posterior probability of linkage (%)
1	+0·42 (MFD188)	72·5	88·8
2	+2·44 (MFD188)	99·6	99·9
3	+0·58 (42D6)	79·2	79·2
11	+2·08 (42D6)	99·2	99·2
16	+0·77 (42D6)	85·5	85·5
30	+1·37 (MFD188)	95·9	95·9
37	+0·60 (MFD188)	79·9	92·3
2000	+0·77 (MFD188)	85·5	94·6

Table 3 *Age of unaffected women at last follow-up, carrier status of* BRCA1 *mutation and lifetime risk of breast cancer in eight families with probable* BRCA1 *linkage*

Family	No. of individuals	Current age of unaffected women (years)	Probability of *BRCA1* mutation (%)	Lifetime risk of breast cancer (%)
1				
Probable carrier	9	16, 18, 26, 27, 27, 27, 30, 33, 56	87·9	82·1
Probable non-carrier	3	30, 38, 41	0·9	13·3
2				
Probable carrier	2	42, 45	98·9	87·2
Probable non-carrier	12	24, 30, 35, 39, 40, 41, 43, 53, 58, 66, 73, 79	1·0	9·8
3				
Probable carrier	0	—	—	—
Probable non-carrier	1	48	0·8	16·4
11				
Probable carrier	2	41, 49	98·2	86·8
Probable non-carrier	9	31, 31, 40, 43, 48, 66, 71, 71, 79	1·0	10·0
16				
Probable carrier	3	39, 41, 66	84·6	80·6
Probable non-carrier	1	74	0·9	14·4
30				
Probable carrier	0	—	—	—
Probable non-carrier	6	42, 48, 53, 55, 57, 68	1·0	11·1
37				
Probable carrier	0	—	—	—
Probable non-carrier	3	32, 39, 42	0·9	12·0
2000				
Probable carrier	3	43, 51, 54	93·7	84·7
Probable non-carrier	2	29, 45	0·9	11·4

Results

Maximal lod score at 42D6 or MFD188, conditional probability of linkage to *BRCA1* and posterior probability of linkage for each of eight breast cancer pedigrees showing probable *BRCA1* linkage are recorded in *Table 2*. *Figure 1* illustrates posterior probability of linkage in all 15 families divided into breast–ovarian and breast cancer (site-specific) families. *Table 3* records the numbers and ages of women unaffected by breast cancer and the percentage probability in favour of *BRCA1* carrier status. Lifetime risks of breast cancer, calculated on the basis of marker data, are also shown.

For demonstration, the methodology employed in calculating the likelihood of *BRCA1* carrier status and lifetime risk of breast cancer in unaffected women in a single pedigree is illustrated below.

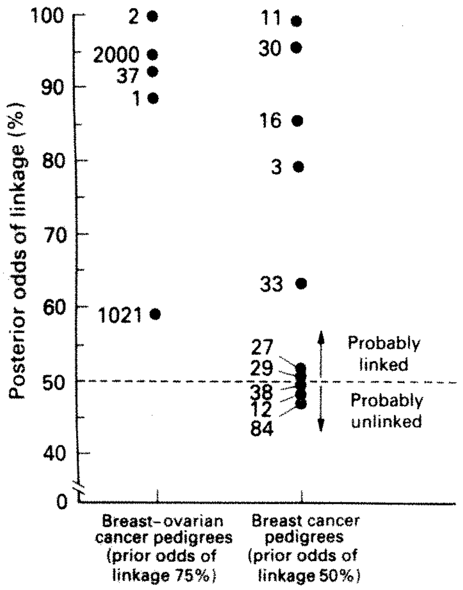

Figure 1 *Posterior probability of linkage in 15 Edinburgh families identified by pedigree number, calculated on the basis of prior odds and conditional odds from 17q marker data*

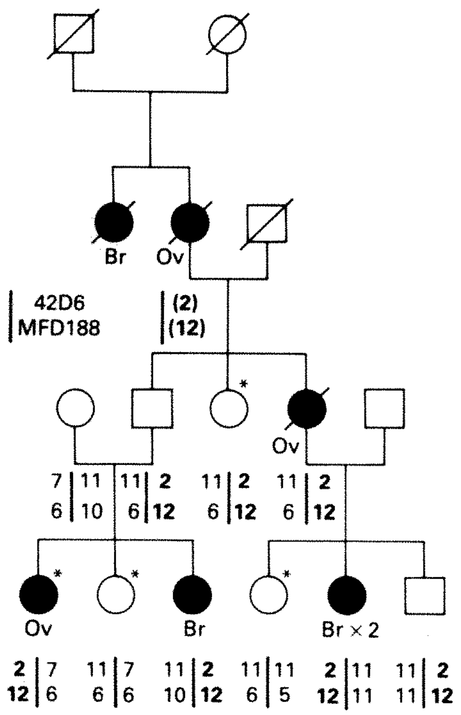

Figure 2 *Edinburgh pedigree 2000 with haplotypes at markers 42D6 and MFD188. Br, unilateral breast cancer; Br × 2, bilateral breast cancer; Ov, ovarian cancer. *Women alive, unaffected by breast cancer and typed at 17q markers*

Pedigree 2000 with haplotypes at 42D6 and MFD188 is illustrated in *Figure 2*. This breast–ovarian cancer subtype family has prior probability of linkage to *BRCA1* of 75 per cent[14]. A maximal lod score of +0·77 was calculated using marker MFD188 at $\theta = 1 \times 10^{-6}$. The percentage conditional probability of linkage (x) is:

$$x = \frac{100y}{y+1}$$

$$= \frac{100(\text{inverse}\log_{10}0{\cdot}77)}{(\text{inverse}\log_{10}0{\cdot}77)+1}$$

$$= 85{\cdot}5 \text{ per cent}$$

The posterior probability of linkage is:

(prior probability in favour × conditional probability in favour) ÷ [(prior probability in favour × conditional probability in favour) + (prior probability against × conditional probability against)]

$$= \frac{(0{\cdot}75 \times 0{\cdot}855)}{(0{\cdot}75 \times 0{\cdot}855) + (0{\cdot}25 \times 0{\cdot}145)}$$

$$= 0{\cdot}946$$

$$= 94{\cdot}6 \text{ per cent}$$

Pedigree 2000 contains four surviving women who have not developed breast cancer (although one had ovarian cancer). Two of these women have inherited allele 2 of 42D6 and allele 12 of MFD188, both of which are associated with malignancy elsewhere in the pedigree. The probability that these women have inherited the mutant susceptibility gene *BRCA1* is the product of:

(posterior probability of linkage to susceptibility gene) and (probability of not having a double recombination event between 42D6 and MFD188).

Double recombination between 42D6 and MFD188 might enable mutant *BRCA1* to be inherited from the gene-carrying parent in association with parental alleles from the non-mutant *BRCA1*-carrying chromosome 17. In no Edinburgh family was double recombination noted between any of four polymorphic markers spanning a region of 17q12-21 that was 12–28 cM in length and which included markers 42D6 and MFD188; more than 100 meioses were typed. Thus, an estimated double recombination rate of 1 per cent is probably maximal for the genomic interval between 42D6 and MFD188. The probability that the *BRCA1* mutation has been inherited in these two women is therefore:

$$(0{\cdot}946) \times (0{\cdot}99) = 0{\cdot}937 = 93{\cdot}7 \text{ per cent}$$

The lifetime risk of breast cancer is a summation of absolute risks attached to carrier status probability. These women may be: (1) mutant *BRCA1* carriers; (2) non-carriers in a *BRCA1*-linked family; or (3) either carriers or non-carriers of a different (non-*BRCA1*) susceptibility gene. *Table 4* shows the calculations necessary to arrive at the lifetime risk of breast cancer, which in these women is 84·7 per cent, a value considerably greater than the 46 per cent risk estimated for first-degree relatives of gene carriers from epidemiological studies without the benefit of *BRCA1* linkage data[9].

Two women in pedigree 2000 have inherited neither allele 2 of 42D6 nor allele 12 of MFD188. In this case, the probability that they have inherited the susceptibility gene *BRCA1* is the product of:

(posterior probability of linkage to susceptibility gene) and (probability of having a double recombination event between 42D6 and MFD188)

$$= (0{\cdot}946) \times (0{\cdot}01) = 0{\cdot}009 = 0{\cdot}9 \text{ per cent}$$

Table 4 *Calculation of lifetime risk of breast cancer in three unaffected women who are probable* BRCA1 *carriers as determined by 17q marker data in pedigree 2000*

Carrier status	Probability of status	Lifetime risk of breast cancer attached to status	Product of status and risk
Mutant *BRCA1* carrier*	0·937	0·88	0·824
Carrier of non-mutant *BRCA1* in *BRCA1*-linked pedigree†	0·946 × 0·01	0·09	0·001
Carrier or non-carrier of a non-*BRCA1* gene‡	0·054	0·415	0·022
Total	1·000	—	0·847

*Where lifetime penetrance of *BRCA1* mutation in 61 probable carriers from eight linked pedigrees is 88 per cent. †Where pedigree probability of double recombination event is 1 per cent and lifetime risk of breast cancer in the general population is 9 per cent. ‡Where lifetime risk of breast cancer in female members of non-*BRCA1*-linked pedigrees is estimated[9] to be 41·5 per cent

Table 5 *Calculation of lifetime risk of breast cancer in two unaffected women who are probable non-*BRCA1 *carriers as determined by 17q marker data in pedigree 2000*

Carrier status	Probability of status	Lifetime risk of breast cancer attached to status	Product of status and risk
Mutant *BRCA1* carrier*	0·009	0·88	0·008
Carrier of non-mutant *BRCA1* in *BRCA1*-linked pedigree†	0·946 × 0·99	0·09	0·084
Carrier or non-carrier of a non-*BRCA1* gene‡	0·054	0·415	0·022
Total	1·000	—	0·114

*Where lifetime penetrance of *BRCA1* mutation in 61 probable carriers from eight linked pedigrees is 88 per cent. †Where pedigree probability of double recombination event is 1 per cent and lifetime risk of breast cancer in the general population is 9 per cent. ‡Where lifetime risk of breast cancer in female members of non-*BRCA1*-linked pedigrees is estimated[9] to be 41·5 per cent

The lifetime risk of breast cancer is again a summation of risks according to that relative probability of carrier status; its calculation is shown in *Table 5*. A lifetime risk of 11·4 per cent in these women is little different from that in the general population of 9 per cent[9].

Calculations of lifetime risk in this paper rely on lod scores computed as part of the linkage program Mendel[15], which derives two-point lod scores at 21 discrete recombination distances. Slightly different risk estimates may be obtained from programs that integrate lod scores over a range of recombination distances and in which multipoint analyses have been utilized.

Discussion

A total of 19 women in five pedigrees had a probability of mutant *BRCA1* carrier status that ranged from 84·6 to 98·9 per cent. The lifetime risk of breast cancer ranged from 80·6 to 87·2 per cent. (Three pedigrees contained no surviving women unaffected by breast cancer with *BRCA1* mutation.) A further 37 women in eight pedigrees had odds of mutant *BRCA1* carrier status that ranged from 0·8 to 1·0 per cent. The lifetime risk of breast cancer ranged from 9·8 to 16·4 per cent. Reassessment of risk on the basis of linkage data is therefore capable of identifying women who might benefit from regular breast screening at a younger age than is currently available in many centres. Conversely, women with a strong family history but a low risk of malignancy as determined by 17q marker data analysis can be identified as unlikely to benefit from early breast screening. In pedigree 1 there are seven probable *BRCA1* gene carriers aged 30 years or less who have a lifetime risk of breast cancer of 82·1 per cent. By extrapolation from disease penetrance figures in 61 probable mutant *BRCA1* carriers from all eight linked families, these seven women will have a 2·5 per cent per annum risk of developing breast cancer between the ages of 30 and 50 years. Three or four of them are therefore expected to develop breast malignancy during this age interval. Pedigree 2 contains two women aged 30 years or less who are probably non-mutation carriers on the basis of 17q marker data. Their lifetime risk of breast cancer is 9·8 per cent and between the ages of 30 and 50 years their risk[9] is only 0·05 per cent per annum. These young women might be spared the worry of regular breast screening in this age interval.

An ethical problem lies in the relative insecurity of linkage analysis data. For example, in pedigree 1, the *BRCA1* gene mutation can be identified with almost 85 per cent certainty. Yet there is still a 15 per cent chance that breast cancer in this family arises in consequence of an alternative (non-*BRCA1*) susceptibility gene, in which case the apparent non-mutant *BRCA1* carriers will be at significantly greater risk than that calculated on the basis of probable *BRCA1* linkage. From an ethical standpoint it may therefore be acceptable to await definitive *BRCA1* gene identification to confirm genetic status before informing the patient of personal linkage results. This course of action can be defended if, as is anticipated, definitive identification of *BRCA1* occurs shortly[17]. *BRCA1* identification will enable all women who require risk assessment to undergo genetic analysis without reference to labour-intensive family linkage studies. It is possible, however, that *BRCA1*, like the adenomatous polyposis coli gene, is of considerable size so that extensive sequencing will be necessary to identify mutations within it. At present, a special case may be made for high-risk women in *BRCA1*-linked families who request advice about the merits of prophylactic bilateral mastectomy. In this situation disclosure of personal linkage results, accompanied by counselling on data interpretation, may enable a more informed decision to be made.

An additional one or two genes that predispose to breast cancer have already been identified. These are the p53 tumour suppressor gene, which may contribute 0·5–1 per cent to the total burden of breast cancer[18–20], and possibly the ataxia telangiectasia gene in heterozygotes for the trait[21,22]. Screening of these breast cancer susceptibility genes together with *BRCA1* may enable a small, well defined, high-risk group of women to benefit increasingly from both regular breast screening, and pharmacological and surgical prophylaxis.

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Significance of circumferential resection margin involvement after oesophagectomy for cancer

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This study examined the influence of tumour involvement of the circumferential resection margin on subsequent local recurrence after oesophagectomy. Fifty patients were studied: 36 men and 14 women of median age 62 (range 44–83) years. Each patient had undergone oesophagectomy at which all macroscopic disease had been removed. Pathological specimens were sectioned tangentially at 0·5–1·0-cm intervals to permit microscopic examination of the circumferential resection margin. Patients were followed and investigated by endoscopy with biopsy and imaging techniques only if symptomatic. Twenty of the 50 specimens demonstrated involvement of the circumferential resection margin. At median follow-up of 36 (range 24–52) months, eleven of these 20 patients had developed histologically proven local recurrence compared with only four of the remaining 30 in whom the resection margin was clear of tumour ($P<0{\cdot}01$)*. Circumferential spread of oesophageal cancer appears to be a significant cause of local tumour recurrence.*

The outlook for patients with oesophageal cancer is poor[1] and overall survival rates at 5 years remain about 5 per cent[2]. Surgical treatment offers the best symptomatic relief[3], but many patients develop local recurrence.

For rectal adenocarcinoma, recurrence is related to failure to remove the tumour completely and involvement of the lateral resection margin is closely associated with subsequent local recurrence[4]. The concept of *en bloc* resection with extensive lymphadenectomy for colorectal cancer is advocated for gastric carcinoma[5,6]. A similar strategy for oesophageal cancer[7] allows low rates of mortality[8], improved survival[9] at 5 years and no local recurrence[10].

This study investigated the significance of tumour involvement of the circumferential resection margin in patients undergoing oesophagectomy for cancer.

Patients and methods

Fifty patients were studied (36 men, 14 women) with a median age of 62 (range 44–83) years. Each patient had undergone oesophagectomy between 1984 and 1989. Preoperative staging included endoscopy, barium contrast study, ultrasonography of the upper abdomen, computed tomography (CT) of the chest and bronchoscopy where indicated. Frozen-section examination of the proximal resection margins was routinely used. None of the patients received adjuvant chemotherapy or radiotherapy. Details of patients were obtained from a retrospective review of case notes and are given in *Table 1*.

The original operative specimen stored in formalin was orientated and pinned under gentle tension to a cork board. The distance from the macroscopic edge of the tumour to the proximal and distal resection margins was measured and the site of the tumour sliced tangentially at 0·5–1·0-cm intervals. Some 2 cm of oesophagus above and below the tumour were included and separate sections taken from the proximal and distal resection margins. All sections were assessed macroscopically (*Figure 1*). Circumferential resection margins were marked with Indian ink to allow histological identification and to prevent false-positive involvement of the margin as a result of poor embedding technique[11].

Measurements were made on each tumour slice of the distance from the tumour edge to the circumferential resection margin and the distance from satellite deposits or lymph nodes involved with tumour to the circumferential margin. The minimum distance between the tumour and the circumferential resection margin was measured by means of a Vernier scale on the microscope stage. Each of the sections was coded and measurements made on two separate occasions; the microscopist was unaware of the clinical outcome. Specimens were positive if tumour extended to within 1 mm of the circumferential resection margin.

Table 1 *Details of patients*

	Circumferential resection margin involvement		
	Positive ($n=20$)	Negative ($n=30$)	Total ($n=50$)
Median (range) age (years)	64 (48–83)	59 (44–77)	62 (44–83)
Sex ratio (M:F)	12:8	24:6	36:14
Site of oesophageal tumour			
Upper third	1 (5)	2 (7)	3 (6)
Middle third	8 (40)	8 (27)	16 (32)
Lower third	11 (55)	20 (67)	31 (62)
Histological type			
Adenocarcinoma	11 (55)	17 (57)	28 (56)
Squamous cell carcinoma	9 (45)	12 (40)	21 (42)
Adenosquamous carcinoma	0 (0)	1 (3)	1 (2)
Oesophagectomy			
Lewis	10 (50)	21 (70)	31 (62)
Transhiatal	4 (20)	5 (17)	9 (18)
Three-stage	3 (15)	3 (10)	6 (12)
Thoracoabdominal	3 (15)	1 (3)	4 (8)
Anastomotic technique			
Hand-sewn	17 (85)	26 (87)	43 (86)
Stapled	3 (15)	4 (13)	7 (14)

Values in parentheses are percentages

Patients were followed and investigated by endoscopy with biopsy and imaging techniques if they became symptomatic.

Statistical analysis

Non-parametric data were compared using the Mann–Whitney U and χ^2 tests. Survival was assessed from operation because the time between diagnosis and surgery was short (less than 4 weeks) in each patient. Life-tables were drawn by the Kaplan–Meier method and differences in survival between patients with and without involvement of the circumferential resection margin calculated by the log rank test[12].

Results

The median distance from the oesophageal tumour to the circumferential resection margin in patients with a margin of

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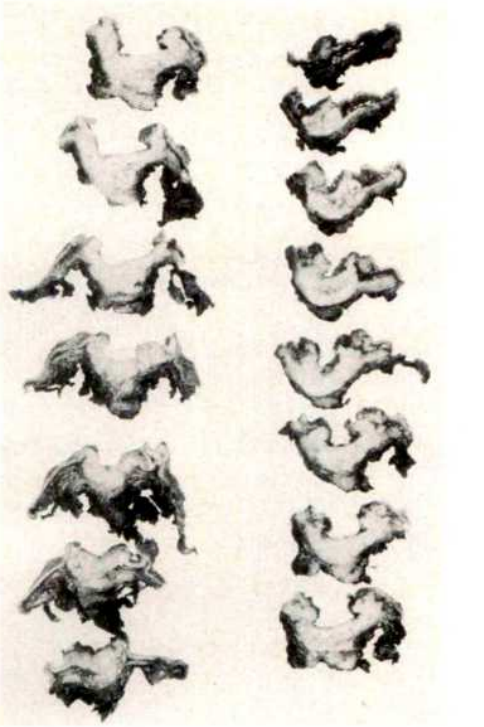

Figure 1 *Tangential slices of oesophagus laid out for inspection and sampling of the circumferential resection margin*

normal tissue included in the resection was 10·0 (interquartile range 6·0–15·5) mm (correlation coefficient R_S between two separate measurements of distance 0·93). The lesion extended to the circumferential resection margin in 20 of the 50 patients, 11 of whom had local tumour recurrence. Of the remaining 30 patients without involvement of the circumferential resection margin, only four had local tumour recurrence ($\chi^2 = 8{\cdot}04$, 1 d.f., $P < 0{\cdot}01$). Of the 15 patients in whom local recurrence occurred, the diagnosis was made by endoscopy with positive biopsy in 11 and by CT of the mediastinum in four. The median length of follow-up was 36 (range 24–52) months.

There was no difference in age, sex distribution, risk factors, preoperative parameters, operative technique, or site, length or histological type of tumour between patients with and without circumferential resection margin involvement.

The median time from operation to diagnosis of local recurrence in the 11 patients with involvement of the circumferential resection margin was 12 (range 4–22) months and the median survival time 15·5 (range 8–24) months. The median time to local recurrence in the four patients without circumferential resection margin involvement was 9 (range 8–13) months and the median survival time of these patients 17·5 (range 9–23) months. The median survival time of the nine patients with involvement of the circumferential resection margin but in whom there was no evidence of local recurrence was 21 (range 13–36) months.

The proximal resection margin was not involved with tumour in any specimen and the median distance of this margin from the tumour in the fixed specimen was 5·0 (range 1·5–8·0) cm. The distal resection margin was also free from tumour in each specimen (median distance 7·8 (range 3·0–30·0) cm). Vascular invasion was present in seven patients and neural invasion in one.

The number of lymph nodes with metastatic involvement shared some correlation with the presence of involvement of the circumferential resection margin ($R_S = 0{\cdot}45$, $P = 0{\cdot}02$).

Four patients had no involvement of the circumferential resection margin but subsequently developed local recurrence of tumour: three had undergone transhiatal blunt oesophagectomy by the Orringer method and, in the fourth, marked vascular invasion by tumour was found.

Of the 20 patients with involvement of the circumferential resection margin, only five survived for 2 years, whereas 14 of the 30 patients who did not have involvement of the circumferential resection margin survived for 2 years (log rank $\chi^2 = 4{\cdot}33$, 1 d.f., $P < 0{\cdot}05$).

Discussion

The idea that depth of penetration of the oesophageal wall by tumour is an independent predictor of prognosis was first suggested[13] in 1982. A staging system based exclusively on wall penetration, lymph node involvement and systemic metastasis has been used to select patients for either *en bloc* or standard oesophageal resection[14].

The present study is open to a number of criticisms. It was non-consecutive and retrospective. Patients were excluded if they failed to survive the operation or were inadequately followed up. There was a predominance of patients with adenocarcinoma of the lower third of the oesophagus. The entire resection specimen was required to allow thorough assessment of the circumferential resection margin. These exclusions may be a potential source of bias.

Although the specimens had been examined previously, they were largely intact and relatively little tissue had been removed for histological examination. The original slides were reviewed to confirm the status of the resection margins. There were adequate amounts of healthy tissue around the tumour in the resected specimens (median clearance 10·0 mm) but this may have been an overestimate as measurements were taken to the furthest point at which healthy tissue was evident. The critical factor, however, appeared to be the presence or absence of tumour at the margin rather than the absolute distance between the tumour and margin.

Recurrence was identified only in patients who became symptomatic and this too may be an underestimate. Although recurrent disease was diagnosed with endoscopy in 11 patients, this probably does not represent implantation or resection-line recurrence; all resection lines were clear at frozen-section and subsequent paraffin-section examinations. CT was performed in seven of the 11 patients and demonstrated extensive mediastinal disease that extended distally and was in continuity with tumour at the level of the anastomosis.

Blunt transhiatal resection of the oesophagus without thoracotomy has been advocated[15], with acceptable morbidity[16]. This technique remains controversial[17] and some argue that it does not permit adequate resection for cancer[7–9,18]. In the present study, three of the four patients in whom local recurrence developed despite clear resection margins had undergone transhiatal oesophagectomy. This small number of patients does not allow statistical analysis.

En bloc resection of the oesophagus with radical lymphadenectomy is associated with favourable survival rates[7,19]. Such resections are more likely to allow complete removal of the tumour. It is possible that *en bloc* resection reduces the likelihood of involvement of the circumferential resection margin and this may partly explain the improved survival[17].

This retrospective study suggests that microscopic involvement of the circumferential resection margin is related to subsequent local recurrence and decreased survival. A prospective study will analyse this hypothesis.

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Announcement

European Surgical Fellowships

The Council of *The British Journal of Surgery* is pleased to announce the availability of European Surgical Fellowships for 1994. Last year four Fellowships were awarded, to Dr Jose Luis Aguayo-Albasini (Spain), Mr R. M. Charnley (Nottingham), Mr S. D. Heys (Aberdeen) and Mr T. G. John (Edinburgh).

It is Council's intention to offer European Surgical Fellowships again in 1994. Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the UK to visit centres in other European countries or surgeons working in other European countries to visit the UK. Applicants must be under 40 years of age and should submit details of their proposed itinerary and its anticipated cost, together with a copy of their *curriculum vitae* and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, by 1 February 1994.

D. C. Carter

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CD4 and CD8 monoclonal antibody therapy: strategies to prolong renal allograft survival in the dog

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The value of CD4 and CD8 monoclonal antibody therapy in tolerance induction has been demonstrated in rodent transplant models. In this paper the immunosuppressive potential of CD4 and CD8 monoclonal antibodies for dog renal allografts was evaluated as a preliminary to tolerogenic studies in this large animal model. Monoclonal antibodies were given for a maximum of 10 days after transplantation. Therapy was stopped prematurely following adverse reactions associated with the recipient developing an antibody response against the foreign (rat) therapeutic monoclonal antibody. Blood trough levels of CD4 and CD8 antibodies indicated that saturating doses were achieved. Although neither CD4 nor CD8 alone prolonged allograft survival (rejection by day 7), combination of CD4 and CD8 antibodies resulted in good graft function for a median of 14 days. The effect of removing circulating T lymphocytes was also assessed using a lytic Thy-1 monoclonal antibody. Alone Thy-1 had little effect but, when combined with CD4, the median allograft survival time was increased to 15·5 days. Reduction of the number of circulating T lymphocytes appears complementary to blockade of CD4 for immunosuppression, while blockade of CD4 combined with removal of CD8 also favours allograft survival.

In rodent models a short course of therapy with monoclonal antibodies to the CD4$^+$ and CD8$^+$ T lymphocyte subsets has been shown to induce tolerance to skin and vascularized grafts across fully allogeneic strain combinations[1–3]. However, tolerance induction in rodents is relatively easy to achieve, as illustrated by the observations that a 2-week course of cyclosporin induces tolerance in PVG rats to DA cardiac allografts[4] whereas a fully immunosuppressive dose of cyclosporin can be given for 100 days to dogs in receipt of renal allografts without altering the tempo of rejection on withdrawal of the drug[5]. Promising tolerogenic therapies thus need to be developed in a large animal model before being considered for clinical application.

The preclinical evaluation of monoclonal antibody therapies may be performed in two ways. One is to use a primate model, selecting monoclonal antibodies raised against human leucocytes that cross-react with the primate leucocytes. Alternatively, species-specific monoclonal antibodies may be generated for a selected large animal model such as pig or dog. Following the latter approach, a panel of rat antidog monoclonal antibodies has been developed. This paper describes the efficacy of CD4 and CD8 monoclonals in prolonging renal allograft survival in mismatched mongrel dogs.

Materials and methods

Monoclonal antibodies

Hybridomas were produced by fusion of rat Y3/Ag1.2.3 myeloma cells with spleen cells from rats immunized with canine leucocytes, thymocytes or concanavalin A-activated lymphoblasts. The resulting monoclonal antibodies were characterized by immunofluorescence, immunoprecipitation, immunohistology and according to their properties in mixed lymphocyte reaction (MLR) and cell-mediated lympholysis assays. Selected hybridomas were grown and injected into pristane-primed (DA × LOU) F_1 rats for the production of ascites. Antibody was obtained by precipitation of the ascites with 50 per cent saturated ammonium sulphate, followed by dialysis into phosphate-buffered saline. Before administration the antibodies were passed through a 2-μm filter. *Table 1* shows the antibodies used, their isotypes and characteristics.

Dogs

Mongrel dogs of either sex weighing between 12 and 24 kg were obtained from this department's breeding colony. Donor–recipient pairs were selected on the basis of MLR-typing data, each pair being a double MLR-defined haplotype mismatch, with a stimulation index of over 25 units in a 6-day MLR. Each dog underwent bilateral nephrectomy and received a single allograft from its pair, transplanted heterotopically into the right iliac fossa with end-to-side vascular anastomoses (6/0 polypropylene) and a ureteroneocystostomy (6/0 polydioxanone).

Table 1 *Monoclonal antibodies used*

Specificity	Antibody	Hybridoma clone	Isotype	*In vivo* effects	Antigen distribution
CD4	YK9-302	YKIX 302.9.3.7	IgG_{2a}	Immunomodulation; partially depleting	T helper cell subset; also on neutrophils in the dog
CD8	YC8-55	YCATE 55.9.1	IgG_1	Depletion and immunomodulation	Cytotoxic T cell subset
	YC8-60	YCATE 60.3.9	IgG_1		
Thy-1	YK9-337	YKIX 337.217.7	IgG_{2b}	Depletion	Peripheral T cells, thymocytes, vascular endothelium especially in renal medulla

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Monitoring

Blood was taken daily for the measurement of both circulating monoclonal antibody levels and host antibody responses to the monoclonal antibody (the antiglobulin response). The assays have been described previously[2-6]. Lymphocyte subsets were determined twice weekly and serum biochemistry three times a week. The survival endpoint was taken as the day the serum creatinine level rose above 300 μmol/l.

Therapy

The antibodies were administered daily by slow intravenous injection. The therapeutic groups are given in *Table 2*. In each group therapy

Table 2 *Results of antibody therapy*

Group	No. of dogs	Antibody specificity	Daily dose*	Time to rejection (days)†	Time to clinical reaction (days)‡	Time to antiglobulin response (days)§
1	2	CD4	20 mg	5, 7	None	None, 6
2	2	CD8	2·5 mg	5, 7	6, 7	4, 4
3	2	Thy-1	5 mg	9, 9	6, 6	6, 6
4	2	Thy-1	5 mg × 2 days	7, 9	None	6, 6
5	4	CD4 CD8	10 mg 5 mg	10, 13, 15, 18	None	CD4: none, none, 5, 13 CD8: 4, 11, 13, 13
6	4	CD4 Thy-1	10 mg 5 mg × 2 days	12, 15, 16, 17	None, none, 7, 8	CD4: 9, 9, 9, 14 Thy-1: 7, 7, 7, 8

*Daily dose of antibody starting 2 days before transplantation and continued to day 10, death or the occurrence of an adverse reaction, with the exception of group 4 which received antibody on the 2 pretransplant days only. †Day after transplantation on which the serum creatinine was ⩾300 μmol/l. On no treatment allograft rejection occurs by day 7. ‡Day after transplantation of an adverse reaction necessitating cessation of antibody therapy. §Earliest day after transplantation on which an antiglobulin response was detected

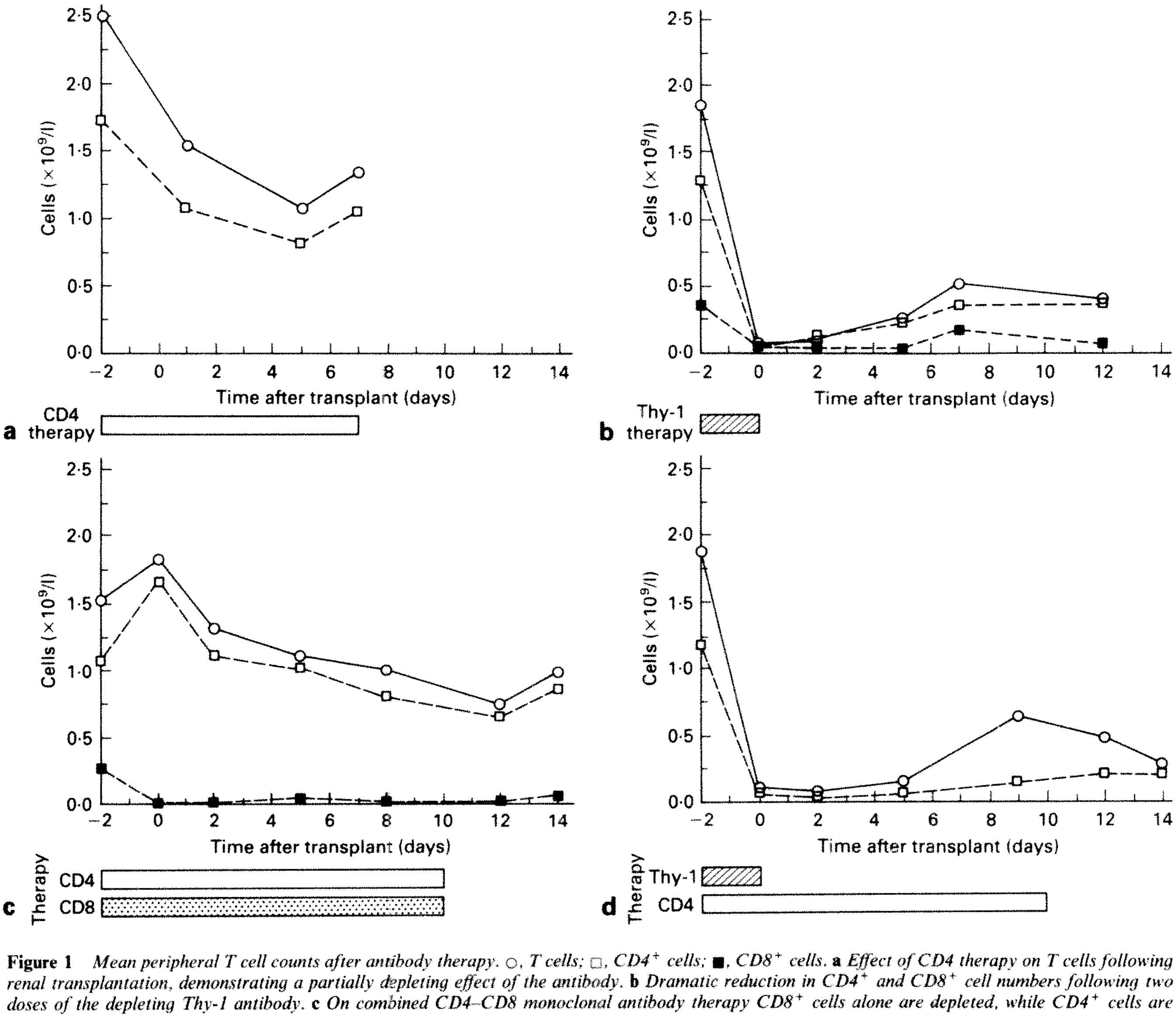

Figure 1 *Mean peripheral T cell counts after antibody therapy.* ○, *T cells;* □, *CD4⁺ cells;* ■, *CD8⁺ cells.* **a** *Effect of CD4 therapy on T cells following renal transplantation, demonstrating a partially depleting effect of the antibody.* **b** *Dramatic reduction in CD4⁺ and CD8⁺ cell numbers following two doses of the depleting Thy-1 antibody.* **c** *On combined CD4–CD8 monoclonal antibody therapy CD8⁺ cells alone are depleted, while CD4⁺ cells are coated with antibody.* **d** *Circulating T cell profile when a short depleting course of Thy-1 antibody therapy is combined with CD4 treatment*

was started 2 days before transplantation. The limited amount of antibody available restricted the duration of therapy and numbers of dogs in each group. The first treatment groups involved antibodies of a single specificity. This was followed by groups receiving either combined treatment with CD4 and CD8 antibodies, or CD4 and Thy-1 antibodies. Therapy was discontinued prematurely on occurrence of an adverse reaction immediately following antibody administration. These reactions, characterized by ataxia, micturition, defecation and loss of consciousness, resolved spontaneously after 10–15 min. Similar anaphylactoid reactions have been reported in dogs receiving polyclonal equine anticanine leucocyte serum[7].

Results

Retrospective control studies have shown that untreated MLR-mismatched mongrels reject renal allografts (creatinine level ⩾300 μmol/l) by day 7, most doing so by day 6.

CD4 therapy (group 1)

A CD4 antibody dose of 20 mg/day failed to prolong graft survival and both dogs rejected the allograft by day 7. Circulating CD4 monoclonal antibody was detectable in the serum throughout at around 10 μg/ml. An antiglobulin response developed in one of the two dogs but neither suffered an adverse reaction (*Table 2*). *Figure 1a* shows the peripheral lymphocyte changes during therapy with a decrease in circulating T cell numbers following transplantation. $CD4^+$ cells were reduced in number and coated with the CD4 antibody throughout.

CD8 therapy (group 2)

Two dogs received a combination of 2·5 mg/day of two different CD8 antibodies (YC8-55 and YC8-60). Again there was no therapeutic benefit and both animals rejected the allograft by day 7. Circulating CD8 monoclonal antibodies were present up to day 4, when both dogs developed an antiglobulin response. An adverse reaction to the antibody occurred on days 6 and 7 respectively. The antibody combination produced over 90 per cent depletion of $CD8^+$ cells from the peripheral blood.

Thy-1 therapy (groups 3 and 4)

When given Thy-1 monoclonal antibody 5 mg/day the recipients exhibited a slight prolongation in allograft survival to day 9. Both dogs had adverse reactions to the antibody requiring cessation of therapy on day 6. The Thy-1 antibody depleted over 90 per cent of circulating T cells, with numbers slowly returning by day 7. A similar depletion of T cells was achieved if only two daily doses were given (group 4; *Figure 1b*). All four dogs developed an antiglobulin response by day 6. Circulating monoclonal antibody was detected only transiently (up to 1 h) after injection.

Combined CD4–CD8 therapy (group 5)

In this group the CD4 antibody dose was reduced to 10 mg/day, which maintained trough levels above 1 μg/ml. The CD4 antibody was combined with a total dose of CD8 5 mg/day, made up of either YC8-55 alone or YC8-55 plus YC8-60 (2·5 mg/day each). Survival time ranged from 10 to 18 (median 14) days. No difference was observed if YC8-60 was included. None of the dogs in this group had an adverse reaction to therapy. All four dogs made an antiglobulin response to the CD8 antibodies, but only two of the four made responses to the CD4 antibody. *Figure 1c* shows the changes in peripheral lymphocytes on combined therapy.

Combined CD4–Thy-1 therapy (group 6)

A combination of CD4 and Thy-1 antibodies was given to four dogs, the Thy-1 being given for 2 days before transplantation to deplete the circulating lymphocyte mass before engraftment, and the CD4 antibody being continued to day 10 (*Figure 1d*). In this group the survival time was extended to a median of 15·5 days. Two dogs had adverse reactions necessitating premature cessation of therapy (days 7 and 8). Antiglobulin responses to both Thy-1 and CD4 antibodies were detected in all four dogs.

Discussion

Donor-specific tolerance to an organ allograft remains a goal of clinical organ transplantation. In rodents such a state can be induced using combinations of CD4 and CD8 antibodies. The antibody requirement varies according to the degree of immunological challenge posed by the donor organ. Non-depleting CD4 therapy alone is sufficient to induce tolerance to major histocompatibility complex (MHC) mismatched cardiac allografts in some mouse models[3,8]. Tolerance to skin allografts is more difficult to induce than that to vascularized grafts. Across multiple minor antigen mismatches, skin graft tolerance can be induced using a combination of non-depleting CD4 and CD8 antibodies, but combinations of depleting and non-depleting CD4 and CD8 antibodies are required where a full MHC mismatch is involved (CBA/Ca recipients of BALB/c skin, $H\text{-}2^k$ into $H\text{-}2^d$)[2].

The ability to induce tolerance is related to the degree of mismatch between donor and recipient, and to the capacity of the recipient's immune system. Even in rodents the amount of surplus capacity behind an immune response is large, such that only a fraction of the normal T cell population is required to reject an allograft[9,10]. Large animals have a large immune system, with a correspondingly large surplus capacity. Thus the induction of tolerance in large animal models and humans is more difficult than in rodents.

The dog has been shown to be a good preclinical model for the evaluation of immunosuppressive therapies: both azathioprine and cyclosporin were assessed in dog renal allograft experiments before being extended into clinical practice[11,12]. In the present study outbred mongrels were selected as a model to assess the efficacy of CD4 and CD8 monoclonal antibodies in prolonging allograft survival. Double-haplotype mismatched donor–recipient pairs gave a high degree of immunological challenge that, if untreated, always resulted in rejection by day 7.

It was found that targeting either inductor or effector arms of the immune response individually with CD4 or CD8 antibodies alone did not alter the tempo of renal allograft rejection, in spite of evidence that adequate monoclonal antibody levels were achieved to ensure coating of the target T cell populations. T cell depletion with the depleting Thy-1 antibody alone also made little difference to allograft survival, in spite of achieving a reduction of over 90 per cent in circulating T cell numbers.

When both inductor and effector arms were targeted together with combined CD4–CD8 antibody therapy, survival was extended to a median of 14 days. This extended survival could be interpreted as the combined therapy being immunosuppressive for the duration of treatment, followed by rapid rejection once therapy ceased. When the excess capacity of the immune system was first reduced by Thy-1 treatment, survival could be prolonged to a median of 15·5 days by CD4 antibodies in the absence of additional CD8. Although this suggests that the efficacy of CD4 is improved by reducing the overall number of circulating T cells, in fact both $CD4^+$ and $CD8^+$ cell numbers are depleted and the effect of Thy-1 may in part be similar to that of CD8 therapy.

The duration of effective monoclonal antibody treatment is restricted by the occurrence of antiglobulin responses directed to the idiotypic and isotypic parts of the monoclonal antibody, preventing binding and hastening clearance from the serum. This has not been such a problem in rodent studies, where CD4 antibodies have been shown to induce tolerance to both themselves and to coadministered antibodies[13]. Similarly, the incidence of antiglobulin responses was less in dogs on CD4 therapy. In the present experiments only one of the two dogs on CD4 alone and two of the four receiving combined CD4–CD8 therapy developed an antiglobulin response. When CD4 therapy was given in conjunction with either Thy-1 or

CD8 the onset of the antiglobulin response to these antibodies was frequently delayed.

The aetiology of the anaphylactoid reaction following administration of antibody occurring between days 6 and 10 is uncertain. It is probably related to the antiglobulin response, especially if this response is mediated by immunoglobulin (Ig) E.

Although allograft survival was prolonged in these studies, a more extensive prolongation will be sought during the development of tolerogenic therapies. One approach would be to increase the dose of monoclonal antibody since 20 mg CD4 (group 1) represents a dose of around 1 mg/kg, contrasting with doses of 4 g/kg used in some rodent studies[2]. The present results indicate that 1 mg/kg CD4 alone was ineffective in this highly mismatched model (stimulation index over 25 units), whereas the same protocol using OKT4A 0·3 mg/kg (a mouse IgG_{2a} antihuman CD4 antibody) in cynomolgus monkeys prolonged allograft survival to a median of 23 days, compared with rejection by day 11 in untreated controls[14]. This beneficial effect using low-dose CD4 alone in cynomolgus monkeys is most likely to relate to the degree of mismatch, since the MLR stimulation indices ranged from 2 to 20 without exclusion of possible shared haplotypes[15], and a wide range of rejection times was noted (8–49 days), although species differences *per se* may be involved. A single high dose (10 mg/kg) of OKT4A on day 0 also resulted in prolonged renal allograft survival (median 36 days) in cynomolgus monkeys, further illustrating the therapeutic efficacy of CD4. The present results indicate that the immunosuppressive effect of CD4 is complemented by combination with other monoclonal antibodies that either deplete or block the immune response.

Other primate experiments have described a beneficial effect when CD4 antibodies were combined with conventional immunosuppression. Jonker *et al.*[16] used a pair of depleting and non-depleting CD4 antibodies (~1 mg/kg each of OKT4 and OKT4A) for 21 days starting at day −2, together with continuous prednisolone and azathioprine compared with prednisolone and azathioprine alone. With CD4 a median of 37 days survival contrasted with a median of 12 days for prednisolone and azathioprine alone.

In conclusion, the present results support the observations in rodent experiments that, as the magnitude of the immunological challenge posed by an allograft rises, increasingly more potent therapeutic monoclonal antibody therapies are required to induce tolerance. The hierarchy of such therapies increases from CD4 therapy alone, through a combination of non-depleting CD4 and CD8 therapies, to a combination involving depleting antibodies. In mismatched mongrel dogs CD4 therapy (1 mg/kg) alone is insufficient to prolong renal allograft survival. Prior depletion of the recipient's lymphocyte mass or combination therapy with CD4 and CD8 antibodies is required. For the induction of tolerance in the dog it is possible that a more prolonged period of therapy involving depleting and non-depleting CD4 and CD8 antibodies and/or additional immunosuppressive drug therapy will be required.

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Patient selection and timing of dynamic computed tomography in acute pancreatitis

Dynamic computed tomography (CT) is the most accurate method for determining the extent of necrosis in acute pancreatitis. Debate exists, however, regarding patient selection and the optimal timing of CT. This study examined selection based on biochemical and/or clinical criteria and the influence of delayed dynamic CT performed 5–10 days after the onset of an attack. A total of 120 patients with acute pancreatitis were studied. Dynamic CT was performed if any of the following criteria were identified: a biochemically severe attack (according to Glasgow criteria) in the first 24 h, C-reactive protein (CRP) level above 120 mg/l in the first 3 days or failure of clinical resolution within 7 days. Of 42 patients selected for CT, five died from multisystem organ failure before day 5. There were no deaths or delayed complications in the 78 patients not selected for scanning. Positive Glasgow criteria alone in the scanned group had a sensitivity for predicting necrosis (as recognized by CT) of 22 per cent and a specificity of 20 per cent. Measurement of CRP level alone had a sensitivity of 26 per cent and specificity of 80 per cent. Failure of clinical resolution had a sensitivity of only 7 per cent but a specificity of 100 per cent. The combination of Glasgow criteria and CRP level had a sensitivity of 44 per cent and specificity of 100 per cent. Delayed complications (pseudocyst, five; infection, six) occurred only in patients with necrosis, and there were two deaths. An 'at-risk' group can be identified for CT on the basis of biochemical and clinical observations. Neither routine nor emergency dynamic CT in acute pancreatitis seems justified.

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The principal benefit of early assessment of severity in acute pancreatitis is the selection of patients who require intensive monitoring and therapy. Early identification of an at-risk group of patients who also have gallstone aetiology allows early endoscopic sphincterotomy with a consequent reduction in mortality rate[1]. Almost all the mortality and morbidity of acute pancreatitis is concentrated in the 25 per cent of patients classified as having severe disease. Those predicted to suffer a mild attack have a very low mortality rate of 1–2 per cent[2–4]. Clinical assessment tends to be subjective and is of limited value in the early detection of severe acute pancreatitis[5]. Single[6–8] and multiple[9] biochemical criteria and peritoneal fluid analysis[10] have all been used as prognostic indicators. Abdominal computed tomography (CT), although highly sensitive for the diagnosis of pancreatitis[11], has not been shown to improve on modified Glasgow criteria (*Table 1*) in predicting the severity of an attack[12,13]. CT is, however, the most accurate method for determining the presence and extent of pancreatic necrosis[14] and is undoubtedly useful in identifying local pancreatic complications[15].

Debate remains regarding patient selection and the optimal timing of CT in acute pancreatitis. The purpose of this prospective study was to identify criteria by which to select patients for CT and to determine whether delaying the scan until the end of the first week has any influence on outcome.

Patients and methods

This study investigated 120 consecutive patients admitted with a diagnosis of acute pancreatitis. The median age was 52 (range 22–87) years in 61 men and 58 (range 21–93) years in 59 women. The aetiology is shown in *Table 2*. Patients were selected for CT by satisfying at least one of three criteria: three or more positive modified Glasgow criteria within the first 24 h, C-reactive protein (CRP) level above 120 mg/l within the first 3 days and failure of clinical resolution within 7 days. The CRP level was based on the work of Mayer *et al.*[6] and Buchler and colleagues[16] implying a 95 per cent chance of necrosis being present above this value. Failure of clinical resolution at 7 days included all patients with persistent clinical features consistent with acute pancreatitis or its complications. In all, 42 patients satisfied these criteria, of whom 37 underwent dynamic contrast-enhanced CT between 5 and 10 days after admission. Patients thought to have a biliary aetiology also

Table 1 *Modified Glasgow criteria for the prediction of severity of acute pancreatitis*

Arterial partial pressure of oxygen	< 8·0 kPa
Serum albumin	< 32 g/l
Serum calcium	< 2·0 mmol/l
White cell count	> 15 × 10⁹/l
Aspartate transaminase	> 200 units/l
Lactate dehydrogenase	> 600 units/l
Blood glucose	> 10 mmol/l*
Blood urea	> 16 mmol/l

* In the absence of diabetes mellitus

Table 2 *Aetiology of acute pancreatitis in 120 patients*

	Mild ($n = 78$)	Severe ($n = 42$)
Biliary	28	20
Alcoholic	25	10
Idiopathic	12	8
Other	13	4

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Table 3 *Value of selection criteria for predicting necrosis identified by computed tomography*

	Necrosis on CT		Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
	Present	Absent				
Glasgow criteria alone	6	8	22	20	43	9
CRP level alone	7	2	26	80	78	29
Glasgow criteria plus CRP level	12	0	44	100	100	40
Clinical criteria alone	2	0	7	100	100	29

CT, computed tomography; CRP, C-reactive protein

underwent endoscopic retrograde cholangiopancreatography (ERCP) and, where appropriate, sphincterotomy within the first 48 h of admission. Necrosis was identified on CT by a consultant radiologist; both intrapancreatic and extrapancreatic necrosis were included. CT was performed on a Siemens DRH scanner (Siemens, Sunbury-on-Thames, UK). Patients were given 20 ml Conray 280 (May and Baker, Dagenham, UK) in 1 litre orange juice beginning 90 min before scanning. Non-enhanced CT was initially performed (8-mm cuts), followed by rapid-sequence scans beginning with a 50-ml bolus of Niopam 300 (Merck Pharmaceuticals, Alton, UK) with injection of a further 50 ml over the next 30 s. Slices of 4 mm were taken with a scan time of 4 s per scan. Fine-needle aspiration of necrotic areas was performed under CT control in all patients with persisting clinical abnormalities at the time of scanning.

Results

All 78 patients classified as having a mild attack of pancreatitis on the three predictive criteria recovered without morbidity or mortality. Of the 42 patients classified as having a severe attack, five died within 72 h of admission. Four of these five were over the age of 80 years and died from multisystem organ failure. One patient died 1 h after ERCP with sphincterotomy and stone extraction, from an acute cardiac event characterized by sustained electrical activity in the absence of cardiac output.

Necrosis was identified by CT in 27 of the 37 surviving patients with severe disease. There were no cases where necrosis could be confidently identified as exclusively extrapancreatic. The ten patients without necrosis recovered without complication. The criteria for CT and subsequent correlation with the presence of necrosis are shown in *Table 3* along with sensitivities, specificities and predictive values. Eleven patients in whom necrosis was identified ultimately came to surgery. Five of these had symptomatic pseudocysts that did not resolve spontaneously or after a single attempt at percutaneous aspiration. Cyst–enteric anastomosis was performed 27–62 days after onset of the attack and all five patients recovered uneventfully. Six patients were found to have infected necrosis with mixed intestinal flora on fine-needle aspiration; all underwent operation designed to remove all necrotic pancreatic and peripancreatic tissue 11–23 days after onset of the attack. (Two patients required a second CT scan with guided aspiration to confirm infection.) There were two deaths after surgery for infected necrosis. The overall mortality rate for the entire series of 120 patients was 6 per cent. In the group with disease predicted to be severe the mortality rate was 17 per cent (18 per cent in patients undergoing surgery).

Discussion

The age–sex distribution of patients with pancreatitis, mortality rate (6 per cent), incidence of clinically apparent pseudocyst (4 per cent) and of infected necrosis (5 per cent) in this study are similar to those of others carried out in the UK[13].

Patients who die from acute pancreatitis tend to do so either early, usually in the first week, from organ failure (adult respiratory distress syndrome, acute renal failure, myocardial insufficiency) or late, from sepsis when necrotic pancreatic and peripancreatic tissues become secondarily infected[17–22]. That early surgery on the pancreas might reduce mortality in the early phase has never been demonstrated[23–27]; there thus seems little justification for recommending emergency CT as a way of defining an acute surgical group that does not exist. It also seems illogical to propose the widespread use of CT as a means of identifying a 'severe' group of patients, since direct assessments of physiological disturbance can be made from the organ systems concerned that are known to identify reliably patients requiring intensive support[3,5–8]. Published opinion regarding the value of CT in this context seems divided[28–33].

On the other hand, the reliability of early biochemical prognostic indicators in identifying patients who will go on to develop late sepsis is open to question. The implication that an acute-phase response protein (CRP) might be highly sensitive in this context merited evaluation. For these reasons, CT was deferred for 5–10 days by which time five patients, whose management we contend would not have been influenced by the result of CT, had died. Since the removal of necrotic pancreatic tissue in the first week of an attack does not improve survival, there seems no reason to use CT to demonstrate necrosis at the time of admission.

Among the 78 patients not selected for CT there were no deaths or late complications. If any of these patients had necrosis, it was only a radiological feature of no clinical relevance. Of the 37 patients who underwent CT, a combination of biochemical tests and clinical assessment identified all those at risk of developing late local sepsis. The inadvisability of relying on Glasgow criteria to predict necrosis in the at-risk group was evident since necrosis was not identified by CT in eight of 26 such patients. Although CRP level is a more useful predictor of necrosis (false-positive results were obtained for only two of 21 patients), the problem with both tests is that, considered individually, they miss an unacceptably high proportion of patients in whom necrosis is recognized by CT. The value of these tests, however, is that, if either or both are positive, there is little chance of missing an at-risk patient, at the expense of a false-positive rate of 29 per cent. If CT is then additionally offered only to patients without biochemical criteria but who remain unwell at the end of the first week of illness, all at-risk individuals may be identified. The performance of ten unnecessary CT scans in 37 patients seems acceptable, bearing in mind that 11 of the 37 ultimately required surgery.

It is apparent that not all patients require a costly CT scan for prognostic purposes and, since the benign nature of the majority of cases can be predicted by biochemical and clinical criteria, CT should be limited to a selected group of patients. Further reductions in the mortality rate attributable to late sepsis might be achieved by refining the selection process for CT further, particularly for patients requiring repeat scans to optimize the nature and timing of subsequent intervention. Routine or emergency CT in all patients with acute pancreatitis cannot be justified.

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Prospective comparison of laparoscopic and conventional anterior resection

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A prospective comparison of laparoscopically assisted (n = 11) and conventional (n = 14) anterior resection in patients with sigmoid colon or upper rectal cancer was carried out. Patients were not randomized: age and the presence of metastases determined the type of surgery. Laparoscopic assistance was used to mobilize the tumour and minimize the abdominal incision. This was achieved in all patients and six of the 11 required only a muscle-splitting incision. The mean(s.d.) operating time was longer for laparoscopic than conventional surgery (205(31) versus *123(26) min, P = 0·01). The mean(s.d.) time to reintroduction of normal diet (2·5(0·2)* versus *3·6(0·3) days, P = 0·01), postoperative analgesia requirement (2·6(0·4)* versus *7·4(2·1) doses of pethidine, P = 0·01) and length of hospital stay (12·3(3)* versus *14·3(6) days, P = 0·08) were less in the laparoscopic group. Histopathological examination of the resection specimens showed similar results for the two procedures. Major complications were few and occurred in a similar proportion of patients treated laparoscopically or conventionally. Laparoscopically assisted anterior resection is technically feasible, adequate tumour excision can be achieved and recovery after operation is enhanced.*

Laparoscopic surgery can reduce the trauma of access and improve recovery after operation, notably in cholecystectomy[1,2]. Similar benefit may derive from laparoscopic bowel surgery[3–5] but the technical problems are greater, including tissue handling, anastomosis and removal of resected material from the abdomen. An abdominal incision is usually required for specimen removal but it can be reduced in size (laparoscopically assisted surgery).

Adequate tissue resection is of utmost importance in colorectal malignancy and must not be compromised by minimally invasive surgery. Some centres have restricted laparoscopic approaches to patients with benign disease and/or requiring limited procedures[3,6], whereas others have concentrated on right-sided lesions[7]. Colorectal cancer is the most common indication for large bowel surgery and 60 per cent of such tumours occur in the rectum and sigmoid colon. Laparoscopic excision of the distal large bowel is likely therefore to have the greatest impact.

This study compares laparoscopically assisted sigmoid colectomy and anterior resection of the rectum with conventional surgery.

Patients and methods

Patients presenting with carcinoma of the sigmoid colon or proximal rectum were studied. Patients were excluded if they had a distal rectal tumour (requiring anastomosis within 5 cm of the dentate line or abdominoperineal resection), a fixed mass palpable rectally or abdominally, or if they had received previous radiotherapy or extensive abdominal surgery. Those aged over 65 years and/or with metastatic disease not treatable by surgery were selected for a laparoscopic procedure. Operation was performed subject to patient agreement and availability of sufficient operating time. Younger patients, including those with three or fewer liver metastases confined to one lobe, were treated by conventional surgery. Patients were not randomized to either type of operation.

Bowel preparation was administered 24 h before surgery and prophylactic broad-spectrum antibiotics prescribed. A urinary catheter and nasogastric tube were used in all patients and surgical drains placed in the pelvis at the end of the procedure. Operating time was measured from the first incision to reversal of anaesthesia.

Laparoscopically assisted surgery

Laparoscopic operations were performed by a team of four surgeons (including the camera operator) with the patient placed head-down in the Lloyd-Davies position. Laparoscopy was performed via a subumbilical incision with four accessory cannulas. Operative steps included: (1) mobilization of the sigmoid colon up to the splenic flexure; (2) division of the inferior mesenteric artery; (3) division of the mesentery including the marginal artery; (4) mobilization of the rectum; (5) division of the bowel distal and proximal to the tumour; and (6) anastomosis. The extent of laparoscopic surgery was determined during the procedure; in this pilot study an incision determined by the position of the tumour was made before step 6. This was usually a suprapubic incision for rectal tumours and in the left iliac fossa for sigmoid lesions.

Conventional surgery

Operations were performed with the patient supine or in the Lloyd-Davies position through a midline abdominal incision.

For both types of surgery complete local tumour excision was carried out and the inferior mesenteric artery ligated as far proximal as possible to maximize lymph node clearance. Specimens were submitted for histological examination; the pathologist was unaware of the method of operation.

After operation patients were prescribed pethidine approximately 1 mg kg^{-1} every 3 h as required or dihydrocodeine tablets 30 mg every 4 h as required. For nausea, metoclopramide 10 mg every 8 h was given orally or by intramuscular injection. Early mobilization was encouraged. The nasogastric tube was withdrawn when drainage was less than 100 ml in 12 h. A fluid diet was started when bowel sounds returned and, if well tolerated, solid food was given thereafter. Pain and nausea were assessed 24 h after surgery using a visual analogue scale (10-cm horizontal line without graduations).

Patients who required only basic nursing and were not sufficiently self-caring to be discharged home were transferred to a convalescent ward. All patients were seen in an outpatient clinic 4–8 weeks after discharge.

Statistical analysis

Results of laparoscopically assisted and conventional surgery were compared using the Mann–Whitney *U* test for variables requiring a

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comparison of central tendency only. For measurements of postoperative recovery with a time trend the Mantel–Cox test was employed.

Results

Eleven patients underwent laparoscopically assisted resection and 14 conventional open surgery. Clinical data are summarized in *Table 1.*

The tumour was fully mobilized in all patients and the blood supply divided in eight of 11 during laparoscopic surgery. A grid-iron incision in the left lower quadrant was used in six patients and a Pfannenstiel incision in five. In one patient sutured anastomosis was performed on the surface and ten underwent stapled intra-abdominal anastomosis (cross-stapling technique with circular stapled anastomosis through the transverse staple line) performed under direct vision through the abdominal incision. One patient had an air leak on testing of the anastomosis, which was rectified by sutures after modest extension of the wound.

At conventional surgery six patients had sutured and eight stapled anastomosis. All anastomoses were air-tight on testing. The mean(s.d.) operating time was significantly longer for laparoscopic surgery (205(31) *versus* 123(26) min, *P*=0·01).

The time to reintroduction of normal diet, postoperative analgesia requirement and length of hospital stay were all reduced in patients undergoing laparoscopic operation (*Table 2*). There was no difference between the two groups in the time to removal of the nasogastric tube or the time at which patients first reported passing flatus. Diet was tolerated earlier by patients treated laparoscopically and intravenous fluids were required for longer after open surgery. At 24 h after operation, pethidine dosage and visual analogue scale scores for pain and nausea showed no differences between the two groups. Subsequent requirement for narcotic analgesia was significantly reduced in patients undergoing laparoscopic resection.

Table 1 *Details of the two patient groups*

	Laparoscopic (*n*=11)	Conventional (*n*=14)
Age (years)*	69 (39–83)	64 (52–88)
Sex ratio (M:F)	5:6	6:8
Weight (kg)*	55 (45–65)	55 (34–75)
Palpable abdominal mass	1	2
Distant metastases	8	5
Tumour distance from anal canal (cm)*	20 (7–40)	15 (7–30)

*Values are median (range)

Table 2 *Details of patient recovery after operation*

	Laparoscopic (*n*=11)	Conventional (*n*=14)	*P*
Time to restart diet (days)	2·5(0·2)	3·6(0·3)	0·008*
Total analgesia (doses of intramuscular pethidine)	2·6(0·4)	7·4(2·1)	0·011†
Length of hospital stay (days)	12·3(3)	14·3(6)	0·079*

Values are mean(s.d.). *Mantel–Cox test; †Mann–Whitney *U* test

Table 3 *Complications occurring in the two groups of patients*

Laparoscopic (*n*=11)		Conventional (*n*=14)	
Major		Major	
Peritonitis (day 5)	1	Pelvic abscess	1
		Hydronephrosis	1
Minor		Minor	
Rectal bleed (day 1)	1	Urinary retention	1
Hypoxia (day 2)	1	Chest infection	1
Wound infection	2		
Total	5	Total	4

Table 4 *Details of resection specimens*

	Laparoscopic (*n*=11)	Conventional (*n*=14)
Dukes' stage		
A	1	0
B	4	9
C	5	4
Carcinoid	1	0
No. of nodes resected*	10 (2–14)	13 (2–18)
Length of bowel resected (cm)*	14 (11–21)	15 (7–25)
Distal resection margin (cm)*†	2·0 (0·5–5)	2·5 (2–5)

*Values are median (range). †Does not include 'doughnut' resected by staple gun. There were no significant differences between the two groups

Complications occurred in similar proportions of each group (*Table 3*). One patient undergoing laparoscopic resection with adhesions from previous surgery developed signs of peritonitis on the fifth day and laparotomy was performed. A perforation in the small bowel was found and repaired; the patient made a full recovery but hospital stay was prolonged to 29 days. After conventional surgery, one patient developed left loin pain at 7 days and unilateral hydronephrosis was demonstrated ultrasonographically. This patient responded to treatment with a temporary ureteric stent.

Histopathological examination of the resection specimens showed no significant differences between the two groups for length of resected bowel, length of resection margins and number of lymph nodes (*Table 4*).

Discussion

Initial reports of laparoscopic bowel surgery[3–12] suggest advantages but have not included comparative data. In the present study patients for laparoscopically assisted surgery were selected, but a higher proportion had metastatic disease than those treated conventionally, favouring the latter group. The results demonstrate enhanced recovery after laparoscopic surgery.

Pain after laparoscopic operation decreased slightly in the first 24 h and was significantly reduced overall, which should allow more rapid return to normal activity. Return to work at 7 days has been reported[3]. The time to return of bowel function (passage of flatus) was similar in both groups but diet was tolerated earlier by patients undergoing laparoscopic surgery. There were no differences in length of hospital stay but this could have been affected by the less advanced stage of disease in patients treated conventionally. The social circumstances of some of our patients dictate a longer stay in hospital after major surgery than in Europe and North America; two-thirds of patients were transferred to a convalescent ward, which prolonged their stay. Hospital stay of 5–8 days after laparoscopic bowel surgery has been reported[3,4,6].

The abdominal incision was considerably reduced in size for laparoscopic compared with conventional surgery and when full mobilization of the tumour and its mesentery was achieved the use of a grid-iron muscle-splitting incision was possible. It should be possible to achieve a macroscopically clear margin of normal tissue, accepting the limitation that the tumour must be mobile[4]. Loss of touch sensation might allow a surgeon carrying out laparoscopy to cut through a tissue plane containing tumour. Lateral resection margins must be examined histologically with great care but there were no significant differences in the standard histological parameters for the two groups of patients. High ligation of the inferior mesenteric artery can be achieved during laparoscopic surgery, particularly if conventional ligatures are used rather than a stapling device. By dividing the distal resection line through the small abdominal incision an adequate margin can be assured by palpation. Contact between tumour and the sides of the incision must be prevented when it is removed, to avoid implantation[12,13].

Laparoscopic bowel resection is technically more demanding than cholecystectomy and there is concern about providing suitable training[14]. Safety is paramount and a small incision must be extended if necessary. Adding a simple procedure such as tubal ligation to diagnostic laparoscopy results in a doubling of the complication rate[15]. One patient in the present series suffered iatrogenic small bowel perforation, a contributing factor being instruments out of the field of view used for retraction. This complication presented on the fifth day after operation, a time at which anastomotic leakage can present or when patients may be fit for discharge. The shortest reported mean stay after elective laparoscopic bowel resection[3] is 3·8 days and life-threatening complications could occur at home. Patient counselling and communication with community medical services are required.

Careful histological assessment and long-term follow-up are needed for the oncological aspects to be more accurately determined. Laparoscopically assisted anterior resection and sigmoid colectomy are technically feasible, adequate tumour resection can be achieved and recovery after operation is enhanced.

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Faecal occult blood screening for colorectal neoplasia in a targeted high-risk population

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A general practice-based programme was initiated in 1987 to identify individuals at high risk of developing large bowel cancer and offer them screening of faecal occult blood. In all, 5298 people from 21 general practices in the Guildford area were offered 7510 screening tests. In total, 5934 tests were completed (compliance rate 79·0 per cent) with 287 positive results (4·8 per cent). Of the patients with positive results, 44 had cancer and 38 polyps. The sensitivity of the test for cancer was 63 per cent, the specificity 96 per cent and the positive predictive value for all neoplasia 29 per cent. The detection rate of 44 cancers per 5934 people screened compares favourably with data from the Nottingham-based screening of an unselected population (0·74 versus *0·23 per cent).*

Recent population screening studies for large bowel cancer in Europe and elsewhere have used a guaiac test for occult blood in the stools (Haemoccult; Rohm Pharma, Weiterstadt, Germany). The positive rates for Haemoccult have varied from 1·0 to 3·7 per cent, with positive predictive values for neoplasia ranging from 32 to 59 per cent and compliance rates from 53 to 74 per cent depending on the method of invitation[1–4].

Patients and methods

In 1987, two general practices matched for population size were approached by a consultant surgeon to set up a targeted screening programme. A flexible protocol was designed to be used by either a doctor or practice nurse in the course of a normal consultation at a health screening clinic or new patient clinic.

A high-risk patient was defined as one over 40 years of age with either bowel or abdominal symptoms or with a family history of one or more first-degree relatives with cancer of the bowel, breast, endometrium, liver, ovary or stomach. Patients with an obvious cause of rectal bleeding, such as untreated haemorrhoids or ulcerative colitis, were not excluded as it was felt that these diagnoses could conceal bleeding from a carcinoma. Family history may identify individuals from 'cancer families' as defined by Lynch *et al.*[5].

Two questionnaires were devised to identify and recruit high-risk individuals into the screening programme; both were given to any patient over 40 years attending the surgery for whatever reason. One was an invitation to general health screening; the other was limited to large bowel screening. A poster was designed for display in the general practice waiting rooms. Credit card style reminders and desk-top reminders containing the protocol and inclusion criteria were also produced. A kit for testing faecal occult blood (FOB) was given to each patient, with written directions for its use. Patients were invited to telephone the surgery for results. Completed kits were returned to the surgery and collected weekly, with record cards. The kits were developed at the hospital and results posted back to the surgery.

Patients with a positive FOB test result were referred for colonoscopy or, in a few instances, fibreoptic sigmoidoscopy plus double-contrast barium enema. Patients' referral letters were identified with a specially designed screening programme stamp to facilitate the earliest possible appointment date for colonoscopy (usually within 1 month).

Individuals with a relevant family history were eligible for recall after 1 year and thereafter every 4 years. Those with a past history of cancer or adenoma were also recalled. Patients with symptoms and no relevant family history were investigated by the general practitioner (GP) or referred to the consultant. Those whose symptoms resolved were discharged from the study. Demographic data and results were entered on a computer database from which patients due for recall were selected at monthly intervals.

Results

In all, 5298 individuals were offered 7510 FOB screening tests; 5934 tests were completed, an overall compliance rate of 79·0 per cent. *Table 1* shows results for the three groups of patients: those with symptoms who had only one test and those with a family history (first and recall results). The compliance rate to recall, which was by postal invitation, was 53·0 per cent, comparable to the 55 per cent obtained by Hardcastle *et al.*[1].

Colonoscopy results for the 287 patients with a positive FOB

Table 1 *Results of screening tests*

	Symptomatic (one test)	Relevant family history		Total
		First test	Recall test	
No. offered	2775	2523	2212	7510
No. completed	2556 (92·1)	2206 (87·4)	1172 (53·0)	5934 (79·0)
No. positive	168 (6·6)	82 (3·7)	37 (3·2)	287 (4·8)

Values in parentheses are percentages

Table 2 *Colonoscopy results*

	Symptomatic (one test)	Relevant family history		Total
		First test	Recall test	
Cancers	35	8	1	44
Cancer detection rate (%)	1·4	0·4	0·1	
Polyps	17	15	6	38
Polyp detection rate (%)	0·7	0·7	0·5	
Other causes of rectal bleeding	45	14	1	60
No abnormality detected	65	37	24	126
Not referred	2	5	3	10
Refused referral or investigation	4	2	1	7
Testing errors*		1	1	2
Total	168	82	37	287

*Tests repeated and found to be negative

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Table 3 *Site and Dukes' stage of screen-detected cancers in 44 patients*

	Dukes' stage			
	A	B	C	Unclassified
Right-sided	3	5	3	1
Left-sided	3	9	4	
Rectal	2	5	5	
Other (stomach, carcinomatosis)				3
No operation (patient refused)				1

test are shown in *Table 2*. The sensitivity of the test for cancer was 63 per cent, the specificity 96 per cent and the positive predictive value for all neoplasia 29 per cent. The detection rate of 44 cancers per 5934 tests was 0·74 per cent. Twenty-two of the 38 individuals with polyps and nine of the 44 with cancer were asymptomatic with a family history of carcinoma.

Table 3 shows the site and stage of the 44 screen-detected cancers. The patient with an unclassified right-sided tumour did not undergo resection because of extensive local spread. Among patients with symptoms there were five Dukes' A tumours, 15 Dukes' B and 11 Dukes' C. In those with a family history there were three Dukes' A tumours, four Dukes' B and one Dukes' C.

Of the 38 polyps detected, 17 were between 1 and 3 cm in size and 21 less than 1 cm. Twenty-one polyps were tubular adenomas, seven tubulovillous adenomas, one a villous adenoma and nine metaplastic. All the metaplastic polyps were less than 1 cm in size.

Interval cancers occurred in 25 patients and 21 of these had a tumour diagnosed within 1 year of a negative FOB test result. Of the 25 patients, 24 were symptomatic at the time of the test. The asymptomatic patient had a strong family history of bowel cancer and was recalled after 1 year but did not wish to repeat the test. She developed carcinoma of the rectum 3 years after her first test. Only one GP felt that a negative test result had delayed referral of a symptomatic patient.

Discussion

The present compliance rate of 79 per cent does not take account of all individuals potentially at risk. Some people would not have read the questionnaire or failed to respond.

Patient compliance may determine the success or failure of a screening programme. The aim of this programme was to maximize compliance by presenting large bowel screening as part of health screening and preventive medicine. The approach to the patient was through the GP or practice nurse rather than by an impersonal letter. A reduced compliance rate between first and recall testing, and between medical and postal invitation, has been documented in previous studies[6].

The overall positive FOB result rate of 4·8 per cent was high for such a programme as four previous controlled trials of Haemoccult have shown positive rates ranging from 1·0 to 3·7 per cent[1–4]. Since the screening occurred in a high-risk group this result may not be unexpected.

Only eight of the 44 cancers were Dukes' A tumours, which demonstrates the prevalence of the condition in the population and the late onset of symptoms. Two of these tumours were found in polyps which were completely excised by polypectomy. Both patients were asymptomatic with a family history.

Only nine cancers were found in patients with a family history, but 43 per cent of polyps in this group were adenomas over 1 cm in size and therefore at risk of carcinoma[7]. The cancer detection rate was lower in individuals with a family history than in those with symptoms, both overall (0·3 *versus* 1·4 per cent) and in the positive group (8 *versus* 21 per cent). This may justify the inclusion of individuals with symptoms and those with a family history in the high-risk group.

There were 25 patients with interval cancers, but in only one was referral delayed by a negative result. This high proportion highlights the shortcomings of FOB testing. All such tests will miss cancers that do not bleed or bleed only occasionally. Studies of immunological tests such as Fecatwin[8] (Labsystems, Helsinki, Finland) and Hemeselect[9] (SmithKline Diagnostics, San Jose, California, USA) have underlined the importance of the balance between sensitivity and specificity. The sensitivity of Haemoccult is adjusted to maintain a low false-positive rate, but in the present study 36 per cent of cancers were missed. In a high-risk group, it may be more appropriate to use a more sensitive test.

The overall cancer detection rate of 0·74 per cent of patients screened was higher than the 0·23 per cent reported from the randomized controlled trial of unselected individuals in Nottingham[1]. The Nottingham figure was similar to that for the present asymptomatic family history group (0·3 per cent).

The sensitivity of the test for carcinoma was only 63 per cent and there were a large number of interval cancers. Disappointingly few Dukes' A tumours were detected, which may reflect both the low sensitivity of the test and the prevalence of advanced disease in the population.

A group of individuals at increased risk of developing large bowel cancer can be identified through a general practice-based screening programme. Compliance is good and the detection rate of cancers is higher than that found from unselected population screening trials.

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Long-term survival after endoscopic transanal resection of rectal tumours

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The outcome and survival of 120 consecutive patients of median age 78 years with rectal tumours who underwent endoscopic transanal resection were assessed. Thirty-eight patients (32 per cent) were treated for large villous adenoma. These patients underwent a median of 2 (range 1–5) resections and the overall 5-year survival rate was 78·2 per cent. Of 82 patients with rectal cancer, 33 (28 per cent of the 120) had tumours amenable to conventional surgery but for the patient's age or infirmity. The 5-year survival rate of these patients was 29·7 per cent. Endoscopic transanal resection was used to palliate the symptoms of 49 patients (41 per cent) with rectal cancer; the 5-year survival rate was 13·7 per cent. Excellent long-term outcome may be achieved with endoscopic transanal resection for patients with benign rectal tumours. This approach also gives acceptable results for selected patients with rectal cancer in whom age, extent of disease or concurrent illness preclude conventional surgical resection.

Curative treatment for patients with rectal carcinoma usually involves *en bloc* excision of the tumour, the mesorectum and its lymphatics to the origin of the inferior mesenteric artery, either as anterior resection or abdominoperineal excision of the rectum[1]. Occasionally, small early rectal tumours are curable by disc excision *per anum*, albeit with a high risk of local recurrence[2]. Elderly patients and, in particular, those with serious comorbidity tolerate major operations poorly[3] and radical surgery is seldom appropriate for those in whom the tumour has progressed beyond cure because of local fixation or distant metastasis. Local excision may also provide worthwhile treatment for patients with large benign rectal tumours.

Endoscopic transanal resection using a urological resectoscope was first proposed in 1979 as a method for palliation of obstructive carcinoma of the rectum[4]. This technique allows resection of extensive rectal adenomas[5–7] and some patients may be cured of rectal cancer by such an approach[8].

Endoscopic transanal resection is a considerably less invasive approach for the treatment of low rectal tumours than conventional surgery and has the benefits of a short postoperative stay, quick recovery, little pain and economy. The technique provides good short-term symptomatic relief[9], but long-term survival data are required before the procedure should be adopted for patients with villous adenoma and localized cancer. The long-term survival of patients undergoing endoscopic transanal resection for benign and malignant low rectal tumours is analysed in this report.

Patients and methods

A retrospective study of patients undergoing endoscopic transanal resection between January 1982 and September 1991 was performed from the operation registers, clinical records and hospital patient administration computer system. Follow-up information was obtained from hospital case notes, general practitioners' records and the Registrar of Deaths.

Operative technique

Bowel preparation comprised a single phosphate enema and, occasionally, two sachets of Picolax (Ferring Pharmaceuticals, Malmö, Sweden). Antibiotic prophylaxis was provided by intravenous cefuroxime 1·5 g and metronidazole 500 mg. Resection was performed using a 36-Fr modified urological resectoscope with continuous glycine solution irrigation as previously described[9].

Patients

Patients were divided into three groups. Group 1 comprised those with histologically proven villous adenoma. In group 2, patients with adenocarcinoma of the rectum in whom clinical assessment and staging suggested that the tumour was amenable to conventional curative resection either refused, or were judged clinically unfit for, major surgery because of age, senility or concurrent disease (American Society of Anesthesiologists grade III or IV). Endoscopic transanal resection was performed with a view to removing all cancer. This approach was considered potentially curative, with the constraints that the tumours were not accurately staged, and that none of the draining lymphatics and little mesorectal fat had been removed. In these patients control of local disease but failure to cure was an acceptable outcome. Five patients with invasive carcinoma in a villous adenoma were included in this group. Group 3 included patients with locally extensive and fixed adenocarcinoma of the rectum, those with distant metastases or those with local recurrence after previous open surgery who were no longer amenable to open excision. In this group endoscopic resection was performed only for palliation.

Statistical analysis

Survival data were analysed by Kaplan–Meier life-table methods[10]. The log rank test was used to determine differences between life-table curves[11]. The proportional hazard and its 95 per cent confidence interval were calculated[12]. Statistical significance was assumed for $P<0·05$.

Results

A total of 120 patients of median age 78 (range 43–92) years underwent 232 endoscopic transanal resection procedures. During the same period, 813 patients underwent open resection of colonic or rectal neoplasms. All tumours resected endoscopically were within 22 cm of the anal verge and 89 per cent within 10 cm. The tumour characteristics are given in *Table 1*.

Morbidity and mortality

Six patients died within 30 days of transanal resection; the operative mortality rate was therefore 3 per cent of operations and 5 per cent of patients. One patient in group 1 died from a myocardial infarction. Five patients with rectal cancer died within 30 days of surgery, two in group 2 and three in group 3. Two patients with rectal cancer died following immediate laparotomy for colonic perforation, and two very frail patients with rectal cancer for whom laparotomy was rejected died from peritonitis after intraperitoneal perforation during transanal

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Table 1 *Characteristics of resected tumours (insufficient data for some patients)*

	Tubulovillous adenoma	Rectal carcinoma	Total
Distance from anal verge (cm)			
1–5	13	44	57
6–10	13	27	40
11–15	5	5	10
>15	0	2	2
Length of tumour (cm)			
1–2	8	5	13
3–5	16	41	57
6–10	6	31	37
>10	1	1	2
Quadrants involved			
1	15	17	32
2	12	25	37
3	2	19	21
4	2	15	17

Table 2 *Complications of endoscopic transanal resection*

	Group 1	Group 2	Group 3	Total
Haemorrhage	3	3	11	17
Perforation	0	1	0	1
Pelvic sepsis	3	2	2	7
Stricture	1	1	3	5
Rectovaginal fistula	0	3	1	4
Urinary retention	3	0	1	4
Total	10	10	18	38

resection. A further patient with rectal cancer died from bronchopneumonia.

There were 38 complications in 23 patients, a morbidity rate of 19 per cent (*Table 2*). Of 17 patients with postoperative haemorrhage, 12 required transfusion or rectal packing. One patient with an intraperitoneal perforation recovered after immediate laparotomy and closure of the perforation. Perforation of the rectum below the peritoneal reflection occurred in most resections for cancer, but only seven patients developed pelvic sepsis as a result. All responded to treatment with antibiotics. Rectovaginal fistulas resulting from tumour invasion and necrosis in all patients developed late in treatment and were often premorbid. Five patients developed stricture following endoscopic resection but were all easily managed by further radial resection of the scar.

Group 1

A total of 38 patients of median age 73 (range 44–86) years underwent 62 transanal resections (range 1–5 per patient); a single resection only was necessary for 28 patients (*Figure 1*). All patients were cured of symptoms by endoscopic resection.

The overall 5-year survival rate for patients with villous adenoma was 78·2 per cent (*Figure 2*) and the disease-specific survival rate 89·2 per cent. One patient aged 86 years died after operation and two (aged 83 and 84 years) died from unrelated conditions. One patient aged 83 years at presentation developed malignant change in a recurrence of villous adenoma and died 41 months after the first transanal resection.

Groups 2 and 3

Some 82 patients underwent 170 transanal resections for rectal cancer; half required more than one procedure (*Figure 1*). Symptomatic relief was achieved for 74 per cent of patients with rectal cancer (*Table 3*). Seven patients subsequently underwent formation of a left iliac fossa colostomy for disabling incontinence. Five patients showed invasive carcinoma on histological assessment of 'chips' of resected villous adenoma removed during transanal resection. One of these patients underwent anterior resection and another abdominoperineal resection.

The 5-year survival rate for all patients with rectal cancer was 20·2 per cent. For patients in group 2, who were treated with transanal resection with intent to cure, the median survival time was 47 months and the 5-year survival rate 29·7 per cent. For patients in group 3, who underwent palliative resection for rectal cancer, the median survival time was 8 months and the 5-year survival rate 13·7 per cent (*Figure 2*).

The 5-year cancer-specific survival rate for all patients with rectal cancer treated with transanal resection was 32·8 per cent. For patients in group 2, the 5-year cancer-specific survival rate

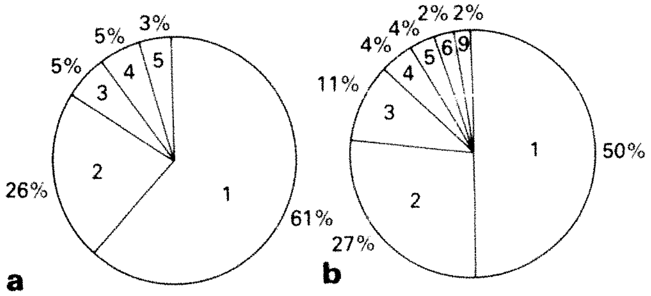

Figure 1 *Number of endoscopic transanal resections undertaken for patients with* **a** *villous adenoma and* **b** *rectal carcinoma*

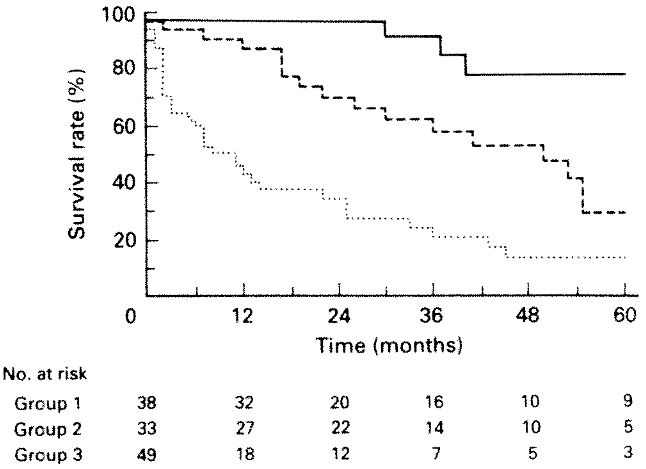

Figure 2 *Survival curves for patients undergoing endoscopic transanal resection for villous adenoma (——, group 1) and rectal cancer (– – –, group 2; ·····, group 3).* $P<0{\cdot}001$ *(group 2* versus *group 3, log rank test)*

Table 3 *Relief of symptoms after endoscopic transanal resection for rectal cancer*

	Abolished	Improved	Unchanged	Not known
Rectal bleeding				
Group 2	8	5	0	1
Group 3	7	5	1	4
Change in bowel habit				
Group 2	5	4	1	0
Group 3	8	7	1	5
Tenesmus or pain				
Group 2	1	0	0	0
Group 3	1	2	2	4
Faecal incontinence				
Group 2	0	1	0	0
Group 3	0	0	1	0

was 48·2 per cent, with a median survival time of 55 months. The cancer-specific 5-year survival rate in group 3 was 21·9 per cent, with a median survival time of 12 months.

Discussion

Patients with rectal villous adenoma present two principal problems: recurrent or residual disease and malignant change. Local or peranal methods of treatment have high recurrence rates of between 10 and 30 per cent[13,14] compared with major resectional surgery. Local excision *per anum*[13] or transanal endoscopic excision[15] are excellent techniques for smaller low lesions. They are more difficult in patients with large, higher villous adenomas and in those with recurrence because the plane of dissection is obliterated at the first operation. Endoscopic transanal resection is a simple treatment, however, and easy to repeat. Most patients in the present series were successfully treated with two procedures. The operative mortality and complication rates compare favourably with those of major surgical resection for patients in this age group.

The incidence of invasive carcinoma in villous adenoma was 12 per cent in this series and 17 per cent in a previous report[13]. Two of these five patients underwent major abdominal resection. The patient who developed invasive adenocarcinoma in a recurrence after transanal resection for villous adenoma illustrates the need for careful histological examination of the resected 'chips'.

Anterior resection and abdominoperineal excision of the rectum for palliation are best avoided if symptoms can be relieved by less traumatic procedures because the operative mortality rate is 21–38 per cent[3,16], recovery slow after major surgery and functional results often poor. The present data confirm a previous report that most symptoms can be controlled by transanal resection[9] and the need for a colostomy delayed or avoided. The survival rate for patients undergoing palliative treatment for rectal cancer was unusually high, with two patients surviving to 5 years after endoscopic resection.

Electrocoagulation is a more time-consuming method of treatment associated with incidences of 22 and 2·5 per cent for postoperative bleeding and perforation respectively[17].

Laser destruction of advanced rectal cancer may be performed as an outpatient procedure and tumours above the peritoneal reflection can be treated. An improvement in 68 per cent of 85 patients treated by neodymium yttrium–aluminium–garnet laser therapy has been reported[18]. In a study by Bright *et al.*[19], however, laser treatment was associated with a 1-month mortality rate of 21 per cent and only 12·5 per cent of patients survived more than 6 months.

Radiotherapy may relieve symptoms in 60–80 per cent of patients with advanced disease[20,21] but may cause rectovaginal fistula, chronic radiation necrosis and stenosis[20].

Advanced age alone is not a contraindication to curative major surgery for rectal cancer with operative mortality rates as low as 4·6 per cent[22] for patients over the age of 70 years and 7 per cent[3] for those over 80 years. The burden of such surgery and the risks of death and complication increase substantially when advanced age is combined with serious comorbidity. An alternative acceptable outcome may therefore be control of local disease without cure.

With the exception of T_1 and T_2 tumours, endoscopic transanal resection seldom removes all rectal cancer. Resection is constrained because little mesorectal fat and none of the draining lymphatics are removed. Tumours cannot be staged accurately for comparative purposes. Endorectal ultrasonography may help to overcome this problem[23,24]. It is difficult to assess the completeness of resection on histological examination. Notwithstanding these limitations, the overall 5-year survival rate of nearly 30 per cent in the present series, and the cancer-specific 5-year survival rate of 48 per cent, are remarkably similar to the 5-year survival rate after open resection of colonic and rectal cancers in the same hospital of 43 per cent[25] and the results of conventional rectal resection reported by some (36 per cent[26] and 44 per cent[27]) but greatly inferior to the 78 per cent from a selected personal series[28]. The unexpectedly good results from an oncologically inadequate operation may arise from selection bias, or repeated thermal injury may inhibit tumour spread. Local surgery may reduce the risks of widespread tumour implantation from open operation and avoids the immunological effects of major surgery and blood transfusion.

This study shows that endoscopic transanal resection is a worthwhile repeatable technique for the treatment of selected patients with rectal cancer and is also a useful alternative to transanal local excision for the treatment of large villous adenoma.

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Short note

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D-dimer: a useful marker of disease stage in surgery for colorectal cancer

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It is widely accepted that malignancy is associated with an increased risk of thromboembolic disease[1], and it has been postulated that anticoagulant treatment may improve prognosis after surgery for colorectal cancer[2]. Tumours have a systemic effect on haemostasis that has been likened to a subclinical state of disseminated intravascular coagulation (DIC). The D-dimer assay is a new test specific for degradation products of a stable fibrin clot, and it has proved to be a sensitive marker of DIC[3]. The aim of the present study was to compare the D-dimer assay with conventional coagulation tests, including antithrombin III activity, for investigation of asymptomatic hypercoagulability in relation to tumour stage and response to surgical trauma.

Patients and methods

The study population comprised 12 patients (six men, six women; mean age 73·1 (range 67–88) years) admitted for curative resection of colorectal carcinoma. The control group was 12 patients (five men, seven women; mean age 67·3 (range 47–83) years) undergoing elective open cholecystectomy. All patients received subcutaneous heparin prophylaxis until mobile.

Venous blood samples were collected into 9:1 (v/v) 3·6 per cent sodium citrate 24 h before and 1, 3, 5, 14 and 42 days after operation. Plasma samples were prepared within 2 h of venepuncture and aliquots stored at −20°C. Antithrombin III activity was determined using Immunochrom reagents (Immuno, Dunton Green, UK) on a LabSystem Coagulometer (LabSystems Group, Basingstoke, UK). D-dimer levels were determined by enzyme-linked immunosorbent assay using AGEN Dimertest Stripwell kits (Porton Cambridge, Newmarket, UK). The normal D-dimer level was determined to be 30–160 ng/ml; the maximum value was given by adding two standard deviations to the normal mean. The thrombin time, prothrombin time and activated partial thromboplastin time (APTT) were measured for each patient. Statistical analysis was performed using the Mann–Whitney *U* test and Fisher's exact test.

Results

Histological examination of resection specimens showed no Dukes' A tumours, five Dukes' B (four moderately, one poorly differentiated) and seven Dukes' C lesions (three moderately, four poorly differentiated).

There was no evidence of thrombosis or bleeding in either group of patients, and all had normal thrombin time, prothrombin time and APTT both before and after operation. Antithrombin III activity was not significantly different between patient groups, and it was not affected by tumour stage. Preoperative D-dimer levels were higher ($P < 0.002$) in patients with cancer. Patients with moderately differentiated Dukes' B

Table 1 *Changes in plasma D-dimer level after operation for benign and malignant disease*

	Before operation	Time after operation (days)				
		1	3	5	14	42
Plasma D-dimer level (ng/ml)*						
Benign (*n* = 12)	70 (33–97)	311 (205–514)	379 (292–467)	374 (288–854)	463 (300–745)	123 (96–134)
Malignant Dukes' B (*n* = 5)	87 (59–220)	533 (228–598)	463 (299–628)	538 (302–668)	489 (299–648)	132 (96–134)
Malignant Dukes' C (*n* = 7)	475 (243–930)	724 (434–992)	565 (323–1088)	526 (175–1352)	508 (300–745)	375 (125–530)
P†						
Benign *versus* Dukes' B	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Benign *versus* Dukes' C	<0·001	<0·005	n.s.	n.s.	n.s.	<0·05
Dukes' B *versus* Dukes' C	<0·02	n.s.	n.s.	n.s.	n.s.	n.s.

*Values are median (interquartile range). †Mann–Whitney *U* test; n.s., not significant

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tumours had low levels of D-dimer, while those with Dukes' C lesions had high levels ($P<0{\cdot}001$). All patients with Dukes' C tumours but only one with a Dukes' B lesion had D-dimer levels above 160 ng/ml ($P=0{\cdot}006$).

Patients with Dukes' B tumours and those undergoing cholecystectomy showed a similar response to operative trauma (*Table 1*). Patients with Dukes' C tumours had a persistently raised D-dimer level after operation, although by day 42 there was a reduction in D-dimer level compared with the high preoperative value ($P<0{\cdot}001$).

Discussion

The D-dimer assay has demonstrated the existence of subclinical hypercoagulability in the absence of changes in other established coagulation parameters. It has been postulated that tumour-derived procoagulant proteases account for tumour-related coagulopathy, and that they facilitate metastasis by forming fibrin strands around circulating tumour cells, enabling aggregates of cells to lodge in the microcirculation[4]. The present study demonstrates a relationship between advanced human colorectal cancer and increased preoperative coagulation activity as measured by D-dimer production. The fall in D-dimer level observed 42 days after resection of Dukes' C lesions may further indicate a direct relationship between tumour burden and haemostatic disturbance, as has previously been demonstrated[5]. D-dimer is potentially useful as a preoperative marker for advanced colorectal cancer and as such may provide a means of selecting patients who could benefit from adjuvant anticoagulant therapy[2].

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Ultrasonographic screening for abdominal aortic aneurysm in an urban community

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As part of the Birmingham Community Aneurysm Screening Project, 3500 men aged 65–75 years from 20 urban general practices were invited for aortic ultrasonographic screening at their own general practitioner's surgery; 2669 (76·3 per cent) attended. Compliance rates varied between catchment areas, from 52·1 per cent for inner-city areas to 89·6 per cent for suburbs. Successful aortic imaging was achieved in 97·3 per cent of scans. Aortic diameter >29 mm occurred in 219 patients (8·4 per cent) and 79 (3·0 per cent) with a diameter >40 mm were referred for vascular surgical assessment; 140 patients with an aortic diameter of 29–40 mm are currently undergoing follow-up by serial ultrasonographic examinations at intervals of 3 months at their doctor's surgery. Risk factor analysis revealed ischaemic heart disease in 21·9 per cent of men with aneurysm, compared with 11·6 per cent in those without ($P < 0{\cdot}001$)*; 18·3 per cent of men with aneurysm had had a previous myocardial infarction and 13·2 per cent had peripheral vascular disease, compared with 7·4 per cent* ($P < 0{\cdot}001$) *and 8·0 per cent* ($P < 0{\cdot}01$) *respectively of those without. No association was found between aneurysm and hypertension or diabetes. Community-based aortic screening is an inexpensive, effective method of diagnosis of aneurysm, with high compliance from the at-risk cohort of an urban population. Such screening programmes may help to reduce the mortality rate from aortic aneurysm rupture.*

The case for ultrasonographic screening to detect asymptomatic abdominal aortic aneurysm (AAA) is strong[1,2], but remains to be proven. Survival prospects following ruptured aneurysm are poor: more than 50 per cent of patients with rupture die before reaching hospital and even for those who arrive at hospital alive operative mortality rates remain high[3–9]. Conversely, the reported mortality rate for elective surgery is 5 per cent or less[4,6,10,11]; following successful aneurysm repair, life expectancy is restored approximately to that of the normal age- and sex-matched population[3,10,11].

Death from rupture of a previously asymptomatic AAA occurs with increasing frequency in men aged >60 years[1,2,12,13]. Furthermore, epidemiological evidence[14] suggests a linear increase in the reported mortality rate from rupture in England and Wales during the past 30 years. While the disease has its greatest impact in men aged 70–74 years, cost-effective screening is likely to be achieved by ultrasonographic examination of the aorta in the 65–74 years age group of men who are young enough to obtain maximum benefit from elective surgical repair[1]. To date, no controlled trial has established that aortic screening can reduce the mortality rate from ruptured AAA in the community, but important elements of any potentially effective screening programme are a high compliance rate from the population at greatest risk of rupture and an accurate method of screening.

In 1989, the Birmingham Community Aneurysm Screening Project was established. The primary aim was to determine the prevalence of ultrasonographically detected AAA and associated risk factors in an unselected group of men aged 65–75 years within the Birmingham metropolitan area. Other objectives included assessment of the feasibility, accuracy and acceptability of aneurysm screening within the primary-care sector of an urban community.

Patients and methods

Twenty-two general practices representing a cross-section of general practitioners (GPs) in Birmingham were invited to participate in the study. Twenty of the 22 practices approached (77 GPs) accepted. Practice size varied from two partners (4000 registered patients) to nine partners (16 000 patients). All men aged 65–75 years on the age–sex register of participating practices were sent a single postal invitation by their GP to attend screening for AAA at the practice surgery. The style of invitation was dictated by individual practices, based on a suggested pro forma that included a brief explanation of AAA, the method of screening and the existence of effective treatment. Where appropriate, translations into other languages, such as Urdu, were included. Non-responders were not followed up.

Ultrasonographic screening was carried out by a single trained sonographer at GPs' surgeries. Each patient was questioned regarding current medication and smoking habit. A specific history of diabetes, ischaemic heart disease (defined as angina requiring treatment with coronary vasodilators), myocardial infarction (with documented electrocardiographic or enzymic changes), peripheral vascular disease (claudication, transient ischaemic attacks or stroke) and chronic obstructive airway disease (requiring regular treatment with antibiotics or bronchodilators) was also obtained. Blood pressure was recorded. In 364 cases, screening was included as part of a 'well person' health check.

Abdominal aortic scans were carried out using a Pie Data 150S portable ultrasonographic scanner with a 3·5-MHz transducer (Pie Data, Maastricht, The Netherlands). Longitudinal and transverse images of the aorta were obtained from the level of the sternum inferiorly to the aortic bifurcation. Longitudinal scans were used to assess aortic morphology and tortuosity. The maximum anteroposterior or transverse diameter was measured from transverse sections taken at right angles to the aorta at each level. No attempt was made to obtain the suprarenal:infrarenal ratio as the suprarenal aorta could not be visualized reliably on all scans.

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The upper limit of normal aortic diameter was defined as 29 mm. This value was derived from a pilot group of the first 550 men aged 65–75 years in the study, in whom a right-handed skew distribution of aortic sizes occurred. The mode of this distribution was 21 mm. Some 17 per cent of patients had aortic diameters >2 s.d. above the mode and 29 mm (3 s.d.) was therefore taken as a better cut-off point for definition of abnormality.

The accuracy of ultrasonographic measurement was established by blinded reproducibility tests[15] and comparison with computed tomography (CT) findings in 24 patients with aortic diameter >39 mm. The mean difference between CT and ultrasonographic measurements was 0·1 mm, showing no bias between methods. The standard deviation of the differences between methods was 1·78 mm, with a standard error on the distribution of differences of 0·37 mm.

When an abnormal aorta was detected the GP was informed and became responsible for subsequent management. All patients with aortic diameter 29–40 mm were offered follow-up by serial ultrasonography at intervals of 3 months at their GP's surgery. Patients with aortic diameter >40 mm were referred for vascular surgical assessment and follow-up. Elective aneurysm repair was routinely offered only to patients with aneurysm diameter >50 mm, unless surgery was contraindicated (for example, because of severe ischaemic heart disease confirmed by preoperative cardiac assessment and measurement of ventricular ejection fraction). Factors taken into account in the repair of AAAs <50 mm in diameter in four cases were the wishes of the patient, a rapid rate of expansion, or symptoms attributable to the aneurysm.

Analysis of risk factors associated with previously undiagnosed AAA was undertaken using the χ^2 test. $P < 0{\cdot}05$ was considered significant.

Results

Of 3500 men sent invitations, 2669 (76·3 per cent) attended for aortic screening. There was marked variation in compliance between catchment areas, rates ranging from 89·6 per cent attendance (2021 of 2256 invited patients) for suburban practices to 52·1 per cent (648 of 1244) for inner-city areas.

Successful imaging of the infrarenal aorta was achieved in 2597 (97·3 per cent) of initial ultrasonographic scans. In the remaining 2·7 per cent the aorta was obscured by obesity or bowel gas. The mean examination time per patient was 7 (range 5–12) min; a cost per scan of £5·35 was calculated on the basis of salary for screening personnel, travel to general practices, maintenance of ultrasonographic equipment and purchase of consumables.

The distribution of aortic diameter in the screened population is shown in *Figure 1*. A diameter >29 mm was found in 219 of 2597 (8·4 per cent) successfully screened patients. A diameter of 29–40 mm was seen in 140 patients (5·4 per cent); they are undergoing serial ultrasonographic examination at 3-month intervals to monitor aneurysm growth. Increases in aortic diameter have been recorded in 46 (32·9 per cent) of these 140 patients during a mean follow-up of 13 months (mean increase 5 (range 2–18) mm). Seventy-nine patients (3·0 per cent) with aortic diameter >40 mm were referred for vascular surgical follow-up. Only two of these had symptoms attributable to the AAA. Up to 3 years after diagnosis, 56 patients have now undergone aneurysm repair, with one postoperative death (from myocardial infarction) within 30 days of surgery (yielding a hospital mortality rate of 2 per cent). No aneurysm detected by screening has ruptured before planned admission for surgery.

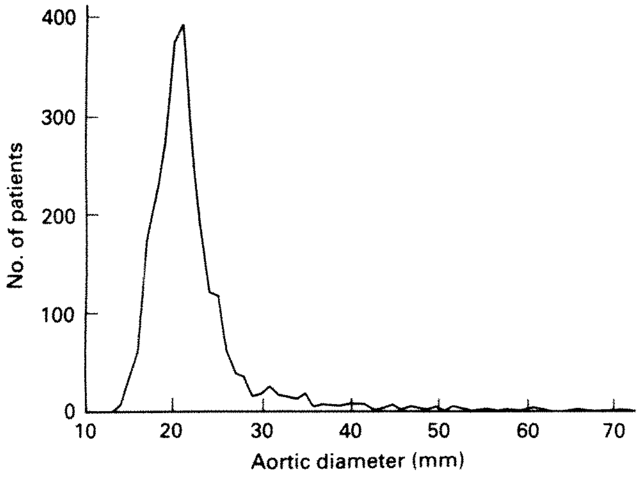

Figure 1 *Distribution of ultrasonographically determined aortic diameter in 2597 men aged 65–75 years*

Table 1 *Prevalence of associated conditions in 2597 successfully screened men aged 65–75 years with aortic aneurysm or a normal aorta*

Associated condition	Aortic aneurysm ($n=219$)	Normal aorta ($n=2378$)	χ^2	P
Ischaemic heart disease	48 (21·9)	277 (11·6)	19·32	<0·001
Myocardial infarction	40 (18·3)	176 (7·4)	31·04	<0·001
Peripheral vascular disease	29 (13·2)	190 (8·0)	7·16	<0·01
Chronic obstructive airway disease	28 (12·8)	205 (8·6)	4·36	<0·05
Diabetes	11 (5·0)	143 (6·0)	0·35	>0·5
Hypertension	42 (19·2)	382 (16·1)	1·47	>0·1
Smoking >10 cigarettes per day	67 (30·6)	418 (17·6)	22·37	<0·001

Values in parentheses are percentages

Table 1 summarizes the prevalence of associated medical conditions in successfully screened patients with AAA or a normal aorta. Of the total screened population, 2612 men (97·9 per cent) had smoked at some time. However, heavy smoking (more than ten cigarettes per day) within 5 years of the time of interview was reported by a significantly greater proportion of men with AAA than by those with a normal aorta.

Discussion

To be effective, a screening programme requires high compliance from the population at risk. An overall attendance rate of 76·3 per cent in the present study compares favourably with results from other screening programmes[16–19], in which the compliance rate ranged from 51·7 to 76 per cent. The high attendance rate can probably be attributed to the invitation to screening being issued by a family doctor known to the patient and to the siting of screening sessions in the close and familiar surroundings of the GP's surgery[17]. Improvement in compliance achieved by GP-based screening has been noted in screening for other diseases[20,21]. A marked difference in the compliance rate between practices located in the inner-city areas (low attendance) and those in suburban areas of Birmingham (high attendance) was observed. This phenomenon has also been reported in breast cancer screening programmes, in which non-attenders tended to be of lower socioeconomic status, were non-partakers of other healthcare services and regarded screening as unnecessary[22]. A further contributory factor to the apparently low rate of compliance in inner-city areas may have been difficulty in maintaining accurate GP patient registers of a transient and relatively mobile population.

In a previous study in the same region, Allen *et al.*[23] found that GPs and hospital doctors who were non-vascular specialists overestimated the risks accompanying aneurysm repair in elderly patients. In this programme, an unforeseen effect of taking screening into the GP's surgery has been an increase, not only in the number of patient referrals for elective aneurysm repair, but also in the audited volume of referrals (27·3 per cent) for other vascular problems.

Accuracy of ultrasonographic measurement is important in screening for AAA, as overestimation of aortic diameter may result in unnecessary anxiety for affected patients and underestimation can leave aneurysms undetected, or lead to lack of appropriate follow-up. Accurate measurement is also necessary for provision of growth data, particularly for small aneurysms for which the potential proportional error of measurement is greatest. The high accuracy of ultrasonographic measurement of aortic diameter compared with values derived from CT in hospital has previously been reported[15]. Specificity of the method was high, with no false-positive diagnoses. It was not possible to assess sensitivity, as men who were apparently normal at first scan have not yet been rescanned. In the present study, all measurements were made by an experienced sonographer using a single ultrasonographic machine. However, accuracy and reproducibility might be adversely affected by employing multiple observers or a variety of types of ultrasonographic equipment in an expanded screening programme[24].

Direct comparison of the prevalence of AAA in the present study with those of other screening programmes is frustrated by important differences in screened groups. In this study, of men aged 65–75 years in a large industrial city, the incidence of aortic diameter >29 mm and >40 mm was higher than that reported from other programmes. In a comparable GP-based study of men of the same age group in a rural area, O'Kelly and Heather[17] found a lower incidence (1·5 per cent) of aneurysm >40 mm, 7·8 per cent of patients having an aortic diameter >25 mm. Collin *et al.*[16], in a hospital-based screening programme targeting men aged 65–74 years in Oxford, using the criterion of a maximal infrarenal aortic diameter at least 0·5 cm greater than the suprarenal diameter or >40 mm, found aneurysms in 5·3 per cent but lesions >40 mm in diameter in only 2·3 per cent. In another recently reported study, Scott and co-workers[18] scanned men and women aged 65–80 years invited by their GPs to attend hospital for screening. Aortic diameter >29 mm was found in 4·3 per cent of the total screened population, but in 8 per cent of men. However, only 2·6 per cent of men had an aneurysm >40 mm in diameter. A higher incidence of aneurysm change of 10·7 per cent was reported in a Swedish population-based study[19] of 364 men aged 74 years who underwent successful ultrasonography in the community of Malmö. Of these, 12 (3·3 per cent) had a maximal aortic diameter >40 mm. The higher incidence in the Swedish study probably reflects the older age of this group of men; 75 years was the upper age limit for screening in the present study.

Not surprisingly, the reported prevalence of AAA is greater in screening studies restricted to high-risk groups: patients with peripheral vascular disease[25,26], hypertension[23,27] and/or coronary artery disease[28,29], and siblings of those with aneurysm[30]. While restricting screening to these groups alone may yield higher AAA detection rates, the overall benefits are likely to be limited as some of these patients will have a poor outlook because of coexisting disease, and many other aneurysms will go undetected.

In common with other reports, patients with aneurysm in the present study had a significantly higher incidence of peripheral vascular disease[16], ischaemic heart disease[19,31], previous myocardial infarction[31] and chronic obstructive airway disease[19,32]. Heavy smokers were also at greater risk of AAA[16,17,19,33]. However, in contrast to some analyses in which hypertension has been reported as a risk factor[23,27], no significant association was demonstrated in the present study; this finding is in accord with those of other population-based screening programmes[16,18,19].

The issue of when to operate on small (4–5 cm) asymptomatic AAAs remains controversial. Some authors advocate serial ultrasonographic follow-up as the risk of rupture of small aneurysms appears to be low[34,35]. Others argue for early elective repair, with low mortality rates, while the patient is relatively young and fit[36,37]. Further prospective data on the growth and outcome of aneurysms <5 cm in diameter are needed. Properly controlled trials of early surgery *versus* serial observation are also essential if the question of when to operate on small aneurysms is to be adequately resolved[38,39].

GP-based ultrasonographic screening of patients aged 65–75 years in Birmingham has revealed an unexpectedly high incidence of asymptomatic AAA. Screening in this way has been well received by patients and GPs alike. It is an inexpensive, effective method of diagnosis with an overall high rate of compliance from this age group of men in an urban population. The incidence of AAA appears to be increasing[14] and broader-based regional or national screening programmes might well contribute to a reduction in unnecessary death from ruptured aneurysm within the community[40].

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Correlation between p53 mutations and antibody staining in breast carcinoma

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Abnormalities of the p53 gene and protein were examined in 81 primary breast carcinoma samples. Using a polymerase chain reaction–single-strand conformational polymorphism (PCR–SSCP) analysis, mutations in p53 exons 5–8 were identified in 13 of 81 tumours (16 per cent) and confirmed by DNA sequencing. Positive staining for p53 protein was detected in ten of 77 (13 per cent) of these tumours using polyclonal CM1 antibody on formalin-fixed tissue. Mutations detected by PCR–SSCP analysis were more common in grade III tumours (P=0·015), but no correlation was found with tumour size, node status or level of epidermal growth factor receptor expression. A p53 mutation was associated with positive antibody staining in only two patients. Positive immunohistochemical staining using a p53 antibody may detect p53 protein expression, but this may not correlate directly with an underlying mutation in the hot spot region examined.

The p53 gene, discovered[1,2] in 1979, encodes a 53-kDa nuclear phosphoprotein with a short half-life and has been mapped[3] to the short arm of chromosome 17. The role of normal or wild-type p53 remains obscure, but the protein may be involved in providing a break to cell cycling at the G1–S phase. Mutation of the p53 gene is the most common genetic lesion identified in human carcinoma, including that of the breast, lung and colon[4–6]. Most mutations characterized so far are missense changes that occur within exons 5–8 in a highly conserved mutation 'hot spot' region.

Many p53 mutations alter the conformation of the protein, resulting in abnormal overexpression[4,5]. In normal cells p53 has a short half-life and such a low steady-state level that it is not detectable histologically[7]. By contrast, mutant proteins have an extended half-life[8] and can be detected by histochemical analysis using antibodies specific to p53. Immunohistochemical methods are relatively simple, can be performed in most hospital laboratories and permit screening of many tissue samples. They are, however, often restricted to fresh-frozen material. Recently developed antibodies that detect p53 protein in formalin-fixed paraffin-embedded sections may replace DNA analysis of tumour tissue if the antibodies are shown to detect mutations.

Previous studies of the role of p53 in human breast cancer have examined p53 protein expression[9], chromosome 17p allele loss[10,11] and p53 antibody staining[4,9]. The present study investigated the correlation between p53 mutations detected at the DNA level and p53 protein expression determined by immunohistochemical methods.

Patients and methods

Fresh breast tumour tissue was obtained from 81 consecutive patients undergoing mastectomy or wide local excision for primary breast carcinoma. The specimen was taken on ice to the pathology department and adjacent tumour sections were obtained for haematoxylin and eosin staining, DNA and immunohistochemical analysis, and determination of epidermal growth factor (EGF) receptor level. Tumour was snap-frozen in liquid nitrogen and stored at −70°C pending DNA analysis.

Polymerase chain reaction–single-strand conformational polymorphism analysis

DNA was extracted from fresh-frozen tissue using caesium trifluoroacetate density-gradient centrifugation and purified as described previously[12]. Exons 5–8 of the p53 gene were amplified using the following oligonucleotide pairs:

CCTGCCCTCAACAAGATGTT/CCTCACAACCTCCGTCATGT
ACATGACGGAGGTTGTGAGG/TCATAGGGCACCACCACACT
GGCTCTGACTGTACCACCAT/GGAGTCTTCCAGTGTGATGA
ATCTACTGGGACGGAACAGC/GAGAGGAGCTGGTGTTGTTG

Polymerase chain reaction was performed in a 25-μl reaction volume containing 100 ng human DNA, 2 mmol/l 2′-deoxynucleotide 5′-triphosphates, 25 μmol/l oligonucleotide primers, 1·5 mmol/l $MgCl_2$ and 0·5 units Taq polymerase for 3 min at 94°C; 30 cycles of 94, 55 and 72°C for 1 min each were performed with precautions to avoid contamination. The polymerase chain reaction–single-strand conformational polymorphism (PCR–SSCP) technique was used to detect mutations in the p53 gene. This recently described method identifies a conformational change in a DNA strand resulting from a single base mutation as a band shift on a non-denaturing polyacrylamide gel[13]. PCR was performed incorporating 0·2 μl [α-^{32}P]2′-deoxycytosine 5′-triphosphate and 1 μl radiolabelled PCR product was denatured in 0·1 per cent sodium dodecyl sulphate–10 mmol/l ethylenediamine tetra-acetic acid at 85°C for 5 min. The sample was electrophoresed on a non-denaturing gel containing 5 per cent acrylamide and 5 per cent glycerol at 18°C, using a water-cooled back plate. A band shift, representing a point mutation, was revealed by autoradiography of the dried gel. A positive control for this analysis was the RG15 adenoma cell line known to have a p53 mutation (CGG to TGG) at codon 282 (kindly supplied by Drs C. Paraskeva and A. Williams, Department of Pathology and Microbiology, University of Bristol Medical School). A negative control, in which DNA was replaced with water, was included in each experiment.

DNA sequencing

Direct PCR sequencing was performed on DNA from three patients that demonstrated band shifts on PCR–SSCP analysis[14]. Oligonucleotide end-labelling was achieved using [γ-^{32}P]adenosine 5′-triphosphate and polynucleotide kinase. End-labelled primer (1 μmol/l) was incorporated with the appropriate 2′,3′-dideoxynucleotide 5′-triphosphate (ddNTP) into four PCR reactions per sample (containing 5 mmol/l ddATP, 5 mmol/l ddCTP, 500 μmol/l ddGTP or 10 mmol/l ddTTP), and the denatured PCR products were separated on a 6 per cent polyacrylamide sequencing gel. The sequence was determined from an autoradiograph of the dried gel.

Immunohistochemistry

Immunohistochemical analysis of formalin-fixed paraffin-embedded tumour sections was performed using the CM1 polyclonal antibody (Novocastria, Newcastle upon Tyne, UK)[15]. The 5-μm deparaffinized sections were incubated with Dulbecco's tissue culture medium containing 15 per cent fetal calf serum for 30 min before overnight incubation with CM1 diluted 1:1500 in Dulbecco's medium containing

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calf serum. A streptavidin–biotin–peroxidase system was used with diaminobenzidine in 0·03 per cent cobalt chloride as chromogen. Haematoxylin was used to counterstain the nuclei. In negative controls antiserum was replaced with buffer; positive controls were breast carcinoma sections that were known to stain strongly positive.

Epidermal growth factor receptor analysis

The level of EGF receptor was determined using a ^{125}I-labelled EGF radioreceptor assay with a cut-off value of 10 fmol per mg protein[16].

Results

Pathology

Tumour was obtained from 81 women of median age 58 (range 33–84) years. The median tumour size was 2·5 (range 0·9–9·0) cm and there were 34 T_1 cancers (42 per cent); 37 per cent of women were node positive.

Histological sections were stained with haematoxylin and eosin, formalin-fixed and embedded in paraffin. Invasive ductal carcinoma was found in 58 patients (72 per cent), lobular carcinoma in eight and undifferentiated carcinoma in four. Ductal carcinoma *in situ* was the main diagnosis in four but was present in 36 tumours overall. Seven patients had miscellaneous tumours. Sixteen tumours (22 per cent) were grade I, 28 (38 per cent) grade II and 29 (40 per cent) grade III[17]. Overall, 55 per cent of tumours were positive for EGF receptor and 41 per cent positive for oestrogen receptor.

Polymerase chain reaction–single-strand conformational polymorphism analysis

Band shifts signifying mutations were detected by autoradiography in 13 of 81 tumours (16 per cent). Mutations were identified in exon 5 in five patients, exon 6 in two, exon 7 in four and exon 8 in two. The mutation was verified and precisely located in two samples by direct DNA sequencing; point mutations were identified in codons 243 (ATG to TTG) and 237 (ATG to ATA). DNA from one patient had a large rearrangement at codon 256; there was a 28 base pair repeat inserted after an A to G mutation.

Mutations detected by PCR–SSCP analysis were more common in grade III tumours ($\chi^2 = 8{\cdot}31$, 2 d.f., $P = 0{\cdot}015$) (*Table 1*). No correlation was found between mutations detected by PCR–SSCP analysis and either tumour size, node status or EGF receptor level.

Immunohistochemistry

Formalin-fixed paraffin-embedded tumour sections for immunohistochemical analysis were available from 77 patients. Sections stained using the p53 antibody were examined independently by two observers with an intraobserver and interobserver variation of less than 5 per cent. Samples were scored with respect to the percentage of staining nuclei in cancer cells. A specimen was regarded as positive if more than 1 per cent of the nuclei stained black.

Positive staining was found in ten of the 77 tumours (13 per cent), but in only two of these patients was a mutation detected by PCR–SSCP analysis. No correlation between the two methods was demonstrated.

Table 1 *Correlation between mutations detected by polymerase chain reaction–single-strand conformational polymorphism analysis and tumour grade*

Tumour grade	Mutation in p53 gene	
	Present	Absent
I	0	16
II	3	25
III	9	20

$\chi^2 = 8{\cdot}31$, 2 d.f., $P = 0{\cdot}015$

Discussion

Abnormalities of p53 have been reported in a variety of common adult tumours including breast and colonic carcinoma, osteosarcoma, lung cancer, ovarian carcinoma and leukaemia[18–22]. The availability of p53 antibodies and relative simplicity of the immunohistochemical method have allowed screening of large numbers of tumour samples, particularly since the introduction of the CM1 antibody, which can be used on paraffin-embedded fixed archival tissue. The advantages of immunohistochemistry over PCR-based techniques are considerable: PCR–SSCP analysis is expensive, time consuming, needs to be strictly controlled to avoid contamination and is not routinely performed in most hospital laboratories. However, the relationship between the two methods and the relevance of positive p53 antibody staining must be determined.

Certain p53 mutations are known to result in a protein with an abnormally long half-life, which may be the result of post-translational stabilization or protein binding. This phenotype is present in about 15 per cent of breast tumours but occurs at a much higher rate in lung and colonic cancer[23]. The CM1 antibodies provide a sensitive method for detection of p53 and up to 50 per cent of breast tumours show positive staining[15]. However, only 13 per cent of tumours in the present immunohistochemical analysis showed positive CM1 staining; this may reflect a reduced sensitivity of the technique when formalin-fixed material is used. Excellent results are obtained with CM1 when tissue is fixed in methacarn, formal saline or phenol–formaldehyde, but several factors reduce the intensity of the p53 reaction. Prolonged fixation periods (over 48 h) in formal saline and the presence of calcium in the fixative are both harmful. The temperature should be kept to a minimum during the fixation–processing procedure, although embedding in wax at 60°C cannot be avoided. The precise conditions of fixation of the archival material used in the present study cannot be guaranteed, but processing may have reduced the accuracy of the immunohistochemistry.

No correlation was found between antibody staining and detection of p53 mutations by DNA analysis. The same discrepancy has recently been noted by others[24,25]. Several explanations may account for the difference in the detection of p53 abnormalities. The antibody method detects p53 protein which has an abnormally long half-life. In tumours that have p53 mutations identified by DNA analysis but no p53 detected immunohistochemically, the mutation may produce a stop signal or a large rearrangement or deletion that prevents expression of the protein. Equally, the mutation may produce a protein with a very short half-life that cannot be detected immunohistochemically. Lack of staining may reflect deletion of both p53 alleles. Tumours that stain positively with the CM1 antibody may have no detectable DNA mutation because homogenized tumour tissue is used for DNA analysis; the normal p53 signal from stromal cells may be amplified and sequenced preferentially and thus obscure the presence of a mutation. The mutation may be present within one of the exons, outside the hot spot region, that was not examined in the present study. Mutations within introns may affect RNA splice sites and produce an abnormal p53 protein, or a mutation in an upstream transcription regulator outside the p53 gene could signal excess synthesis of a normal protein. Immunostaining using CM1 may detect p53 protein expression, but this might not be a direct consequence of, or representative of, an underlying mutation in the p53 gene. Stabilization may result from abnormalities of the p53 breakdown pathway, which would also result in higher p53 concentrations.

In this study, p53 abnormalities detected by PCR–SSCP analysis were associated with high-grade breast tumours. It has been shown that p53 mutations arise relatively late in neoplastic progression and may correlate with increasing dysplasia, malignant transformation or increased tumour aggressiveness. This finding suggests that a p53 mutation should be a useful prognostic marker for later stages of breast carcinoma if techniques for DNA analysis become routinely available.

Immunohistochemical detection of p53, a relatively inexpensive and easily controlled method that can be performed in most clinical laboratories, remains a valuable investigation. Detection of stabilized p53 protein may be more important than identifying a mutation if stabilization is responsible for loss of tumour suppressor ability. Examination of the remaining exons of the p53 gene might clarify these results, and further studies that encompass DNA analysis and immunohistochemistry would be valuable.

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Resting energy expenditure in patients undergoing transhiatal or transthoracic oesophagectomy for carcinoma of the thoracic oesophagus

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Resting energy expenditure (REE) was studied in five patients undergoing transhiatal and in 14 undergoing transthoracic oesophagectomy for carcinoma. All resections were performed with an intention to cure. REE was measured by indirect calorimetry before operation and on days 1, 3, 5 and 7 after surgery. Following transthoracic oesophagectomy, REE increased significantly on days 1, 3, 5 and 7 after operation, and on day 7 the value was significantly higher ($P < 0{\cdot}05$) *than that obtained after transhiatal surgery. Energy expenditure following transhiatal oesophagectomy is lower than that after transthoracic oesophagectomy; this may be a result of reduced surgical stress.*

The primary therapeutic goal in patients with oesophageal carcinoma is prompt and effective palliation[1,2]. Surgical resection and reconstruction are associated with appreciable morbidity and mortality rates. Transhiatal oesophagectomy, without thoracotomy, has been advocated to decrease operative morbidity[3]. Controversy exists regarding the relative safety of transhiatal oesophagectomy without thoracotomy and whether this is an appropriate 'cancer operation' compared with transthoracic oesophagectomy with lymph node dissection in patients with carcinoma of the thoracic oesophagus[3,4]. Transhiatal oesophagectomy is associated with higher morbidity and mortality rates than thoracotomy[5,6]. There may be a difference in the magnitude of surgical stress between the two procedures.

This study examined the difference in surgical insult between these two procedures by measuring the resting energy expenditure (REE) by indirect calorimetry. Because REE increases during acute illness, injury and surgery[7], differences in energy expenditure might reflect the extent of physiological insult in patients undergoing oesophagectomy.

Patients and methods

Patient selection

Nineteen men with carcinoma of the thoracic oesophagus underwent either transhiatal or right thoracotomy with reconstruction. All carcinomas were of squamous cell origin. Patients with diabetes mellitus were excluded. Transhiatal oesophagectomy without thoracotomy was performed in five patients. With a single exception, transhiatal oesophagectomy was chosen in patients with stage 0 or I cancer of the oesophagus, assessed by tumour node metastasis staging[8]. Fourteen patients underwent transthoracic oesophagectomy. Staging of the carcinoma after operation indicated that three patients had stage 0, five had stage I, seven had stage IIA and four had stage IIB disease. In the 14 patients undergoing transthoracic surgery, total removal of the tumour and adjacent lymph nodes was achieved and the surgery was considered curative.

Resting energy expenditure

REE was measured with the patient lying at rest before operation and on days 1, 3, 5 and 7 after surgery. The preoperative measurement was performed in the morning after an overnight fast. Nursing procedures such as physiotherapy were not permitted before the measurements.

A commercially available portable system, the RM300 (Minato Medical Science, Osaka, Japan), was used for REE determinations. This device measures the partial pressures of oxygen and carbon dioxide in expired air using a zirconium oxide oxygen analyser and an infra-red carbon dioxide analyser[9]. Measurements were performed continuously, with averages obtained for at least 10 min, at 2-min intervals.

REE was calculated using the modified van de Weir[10] equation:

$$\text{REE (kJ day}^{-1}) = 16{\cdot}3 \times \dot{V}_{O_2} + 4{\cdot}6 \times \dot{V}_{CO_2}$$

where $\dot{V}_{O_2}$ is oxygen consumption (l day^{-1}) and $\dot{V}_{CO_2}$ carbon dioxide production (l day^{-1}). Basal energy expenditure (BEE) was calculated using the Harris–Benedict[11] method to normalize for age, height and weight.

Surgery

In both operative procedures, end-to-end anastomosis between the cervical oesophagus and gastric tube was performed using a double-layered running suture, and pyloroplasty and feeding jejunostomy were carried out.

Of the five patients undergoing transhiatal surgery, one had oesophagogastric anastomotic leakage and another a wound infection. Of the 14 patients undergoing right thoracotomy, one had disruption of the oesophagogastric anastomosis and two developed wound infection. The leak was small and followed shortly by drainage from the neck incision. No patient developed sepsis or a systemic complication. Both leaks closed without further surgery and these patients were considered suitable for inclusion in the study. There were no operative or hospital deaths.

Statistical analysis

Data are presented as mean(s.e.m.). Analysis of variance (ANOVA) with repeated measures was used for comparison of REE data. ANOVA was followed by Scheffé's F test to detect intergroup differences. The Mann–Whitney U test was used for comparing patient details, length of operation, amount of blood loss and nutritional support. Differences between the incidence of infection, anastomotic leakage and wound infection related to operative procedure were analysed using the χ^2 test. $P < 0{\cdot}05$ was considered significant.

Results

Table 1 gives patient details. There was a significant difference in age between the two groups ($P < 0{\cdot}05$). No differences were found between groups in terms of weight at the time of surgery, weight expressed as a percentage of usual weight or BEE. There was no significant association between the operative procedure and the incidence of infection, anastomotic leakage or wound infection ($P = 0{\cdot}42$). No patient developed sepsis during the study. One patient had an additional carcinoma of the stomach, and colon was used for restoration of intestinal continuity.

The mean(s.e.m.) operating times for transhiatal and transthoracic oesophagectomy were 225(22) and 404(16) min respectively ($P < 0{\cdot}005$). There was no significant difference in the mean(s.e.m.) blood loss between transhiatal and transthoracic

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Table 1 *Patient details*

Patient no.	Age (years)	Weight (kg)	Percentage of usual weight	BEE (kJ day^{-1})	Site of tumour	Stage	Postoperative complications
Transhiatal group							
1	75	60	92	5058	Lower thoracic	IIA	None
2	62	75	100	6247	Mid-thoracic	0	None
3	68	47	100	4376	Lower thoracic	I	None
4	77	44	100	3870	Lower thoracic	I	Anastomotic leakage
5	78	54	100	4494	Lower thoracic	0	Wound infection
Mean(s.e.m.)	72(3)	56(6)	98(2)	4807(406)			
Transthoracic group							
6	52	54	100	5263	Lower thoracic	IIA	None
7	52	54	84	5410	Upper thoracic	I	None
8	67	56	97	5130	Mid-thoracic	IIA	None
9	67	67	100	5640	Lower thoracic	I	None
10	40	65	100	6548	Lower thoracic	IIB	None
11	62	53	95	4983	Lower thoracic	IIB	None
12	75	60	100	4966	Mid-thoracic	IIB	None
13	64	51	100	4770	Mid-thoracic	0	None
14	57	55	100	5297	Mid-thoracic	IIA	None
15	56	67	100	5950	Mid-thoracic	IIA	None
16	54	59	100	5535	Mid-thoracic	I	None
17	50	57	100	5485	Mid-thoracic	IIB	Wound infection
18	68	52	96	4569	Lower thoracic	IIA	Wound infection
19	64	46	87	4389	Lower thoracic	IIA	Anastomotic leakage
Mean(s.e.m.)	59(3)	57(2)	97(1)	5280(151)			

BEE, basal energy expenditure calculated by the Harris–Benedict formula

Table 2 *Nutrition administered*

	Time after operation															
	Day 1				Day 3				Day 5				Day 7			
	NPC	AAs	Fat	Glucose	NPC	AAs	Fat	Glucose	NPC	AAs	Fat	Glucose	NPC	AAs	Fat	Glucose
Transhiatal group ($n = 5$)	42·3(2·5)	0·8(0·3)	0·03(0·03)	2·4(0·1)	72·4(12·1)	0·9(0·2)	0·2(0·1)	3·8(0·7)	90·4(11·3)	1·1(0·1)	0·2(0·1)	4·9(0·8)	93·7(10·5)	1·1(0·1)	0·2(0·1)	5·1(0·7)
Transthoracic group ($n = 14$)	52·7(6·3)	0·3(0·1)	0·07(0·04)	3·0(0·3)	77·4(5·4)	0·9(0·1)	0·2(0·1)	4·3(0·3)	99·2(4·6)	1·1(0·1)	0·3(0·1)	5·3(0·3)	115·9(7·5)	1·3(0·1)	0·4(0·1)	6·0(0·4)

Values are mean(s.e.m.). NPC, non-protein calories (kJ kg^{-1} day^{-1}); AAs, amino acids (g kg^{-1} day^{-1}); fat (g kg^{-1} day^{-1}); glucose (g kg^{-1} day^{-1})

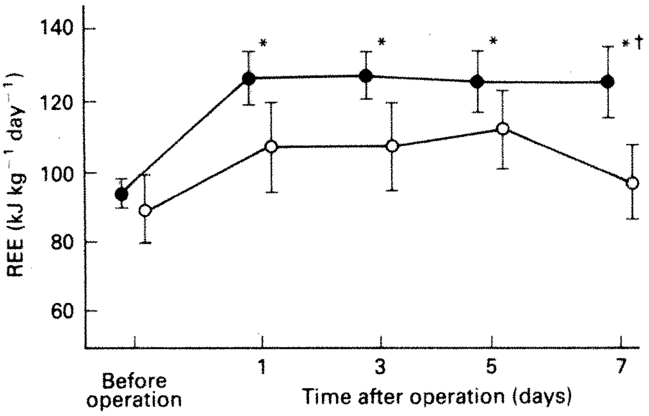

Figure 1 *Changes in the resting energy expenditure (REE) of patients undergoing transhiatal (○) or transthoracic (●) oesophagectomy for carcinoma.* $^*P < 0{\cdot}05$ versus *the preoperative value;* $^\dagger P < 0{\cdot}05$ versus *transhiatal oesophagectomy on day 7 (repeated-measures analysis of variance)*

procedures (467(156) *versus* 748(81) ml). All patients undergoing transthoracic oesophagectomy required mechanical ventilatory support, for a mean(s.e.m.) of 4·1(1·7) days after operation. By contrast, four of the five patients undergoing transhiatal oesophagectomy did not require mechanical ventilation. The patient who required prolonged ventilatory assistance had chronic obstructive pulmonary disease and received support for 30 days.

Postoperative nutritional support is shown in *Table 2*. All patients received total parenteral nutrition in the postoperative period. Feeding via a jejunostomy was begun after the resumption of bowel movement in some patients during the study period.

Changes in the REE of the two groups are shown in *Figure 1*.

Discussion

REE is higher following transthoracic than transhiatal oesophagectomy. Increases in REE have been reported after injury, sepsis and major burns. Patients undergoing major surgery have a rise of up to 24 per cent above the predicted

REE[12]. Because a significant increase in energy expenditure was found after transthoracic oesophagectomy, surgical stress induced by this procedure is likely to be greater than that induced by the transhiatal approach.

Energy expenditure depends on age, nutritional status, energy intake, ambient environmental temperature, and the degree and type of stress[13]. Progressive increase in tumour size is associated with an increase in oxygen consumption[14].

The possibility that the two groups studied were not comparable must be considered. The study was not randomized and there were significant differences in age, tumour stage and patient number between the groups. Transhiatal oesophagectomy was selected for patients in whom the cancer did not invade the surrounding tissues as demonstrated by computed tomography of the mediastinum. Differences in the magnitude of surgical stress between the two groups probably account for the altered REE, for the following reasons.

First, nutritional status and the ambient environmental temperature were identical in the two groups. Second, the difference in REE between the groups before operation was 6·7 kJ kg^{-1} day^{-1}. This is less than the mean difference between groups for REE measured after surgery: day 1, 19·7; day 3, 18·8; day 5, 11·7; and day 7, 31·4 kJ kg^{-1} day^{-1}. Therefore, the observed difference in energy expenditure could not be explained by the age difference between the two groups.

Third, energy expenditure increases following ingestion or intravenous infusion of nutrition as a result of nutrient- or diet-induced thermogenesis[15]. Giovannini *et al.*[16] have shown that 18–25 per cent of REE may come from intravenous administration of nutrients. As the mean difference between the groups in non-protein calorie administration on day 7 after operation was 22·2 kJ kg^{-1} day^{-1}, diet-induced thermogenesis could account for a maximum of 5·4 kJ kg^{-1} day^{-1}. The difference between the groups in REE measured on day 7 after operation was 31·4 kJ kg^{-1} day^{-1}, and it is therefore not plausible that nutrient-induced thermogenesis played a significant role in the observed difference in energy expenditure.

Fourth, the effect of differences in the type of cancer[17] is not relevant because a homogeneous group was studied. The presence of tumour clearly influences host metabolism. Luketich *et al.*[18] reported that REE normalized or remained stable following curative surgery (with no gross evidence of postoperative tumour), while it was hypermetabolic after palliative resection. No patient in the present study had gross evidence of residual tumour after oesophagectomy, making it unlikely that postoperative REE was affected by the presence of tumour.

Finally, transhiatal oesophagectomy took 3 h less to perform and required less blood transfusion than the transthoracic procedure. Postoperative ventilation was required more frequently in patients undergoing transthoracic oesophagectomy. These parameters support the concept that thoracotomy with extended lymphadenectomy is associated with more extensive surgical stress than transhiatal oesophagectomy.

Yamanaka and co-workers[19] have also reported that transhiatal oesophagectomy without thoracotomy involves less physiological insult than radical oesophagectomy with *en bloc* lymph node dissection in the treatment of oesophageal carcinoma.

The REE of patients undergoing transhiatal oesophagectomy is lower than that of those undergoing transthoracic surgery with lymph node dissection. The smaller increase in REE following transhiatal oesophagectomy probably represents reduced surgical stress.

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Continuous single-layer serosubmucosal anastomosis in the upper gastrointestinal tract

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In a 4-year period, 100 anastomoses in the upper gastrointestinal tract were fashioned using a single serosubmucosal layer of continuous polydioxanone. One patient required revisional surgery because of anastomotic stricture after partial gastrectomy, but there was no other complication related to the anastomosis. This technique is simple, safe and quick to perform.

The single-layer serosubmucosal anastomosis has a good track record, both in the lower[1] and upper[2] gastrointestinal tracts, but in most series an interrupted technique has been employed. Although Irwin and colleagues[2] used a continuous suture in a proportion of cases, the precise operative technique is not widely known and does not appear to have been described previously. In this paper a method for performing anastomosis in the upper gastrointestinal tract using a single continuous serosubmucosal layer is detailed and a prospective audit of 100 such operations presented.

Patients and methods

Anastomotic technique

The following description is based on a dependent gastrojejunostomy, but the procedure can easily be adapted for the other types of anastomosis listed in *Table 1*. The first step was to make longitudinal enterotomies in both the stomach and jejunum. Major bleeding points were then secured with careful diathermy, but minor bleeding was not a problem because a true appositional serosubmucosal continuous suture is haemostatic. A 3/0 polydioxanone (PDS; Ethicon, Edinburgh, UK) suture on a 25-mm round-bodied needle was then brought through the serosubmucosal layer of the jejunum from a point about 4 mm away from one end of the enterotomy to the cut edge, and then back through the stomach in a similar fashion, leaving the well defined mucosal layers of both organs undisturbed (*Figure 1*). The suture was tied, leaving a 10-cm tail held with an artery forceps, and the needle passed under the knot ready to start the posterior layer of the anastomosis. Suturing proceeded along the posterior aspect of the anastomosis, with needle bites 4 mm deep and 4 mm apart (*Figure 2*). Holding the mucosal layer alone with an atraumatic dissecting forceps helped to define the serosubmucosal layer for accurate placement of the needle.

When the corner had been passed (*Figure 3*), the direction of suturing ideally continued unchanged (*Figure 4*) but, if this was awkward, a single Connell stitch was placed so that a natural forehand movement could be used to complete the anterior layer. After placing the last stitch, the two ends of suture material were simply tied together and the patency of the anastomosis checked by palpation. This technique gave a neat result with no risk of mucosal protrusion, and it could be executed rapidly without compromising precision.

Patients

Over a 4-year period, 100 upper gastrointestinal anastomoses using the continuous serosubmucosal technique were fashioned in 75 patients. All operations were performed by, or carried out under the direct supervision of, a single surgeon. The suture material used was 3/0 polydioxanone in all cases except for four end-to-end pancreatojejunal anastomoses in which 3/0 polypropylene (Prolene; Ethicon) was employed. The types of anastomosis and their indications are detailed in *Table 1*.

In all cases a midline abdominal incision was used and the wound edges were covered by wound towels and a plastic 'ring' wound protector. Perioperative intravenous antibiotic prophylaxis (cefotaxime 1 g) was routinely used and at the end of the procedure the peritoneal cavity was lavaged with 500 ml saline containing tetracycline 500 mg. The fascial incision was closed with no. 1 PDS, and the skin using a variety of techniques.

Table 1 *Details of 100 anastomoses performed in 75 patients*

Operation	No. of anastomoses
Gastrojejunostomy	
For benign pyloric stenosis	5
For inoperable distal gastric malignancy	10
For inoperable pancreatic malignancy	8
After partial gastrectomy for gastric malignancy	21
After antrectomy for bleeding duodenal ulcer	5
After antrectomy as part of biliary diversion	2
After antrectomy as part of Whipple's operation	4
End-to-side jejunostomy (Roux-en-Y)	
After total gastrectomy	12
As part of biliary diversion	4
Side-to-side enteroenterostomy	
Jejunojejunostomy with cholecystojejunostomy	10
Ileoileostomy for bypass of malignant obstruction	3
Ileocolostomy for bypass of malignant obstruction	2
Cholecystojejunostomy	
For bypass of pancreatic malignancy	10
End-to-end pancreatojejunostomy	
As part of Whipple's operation	4

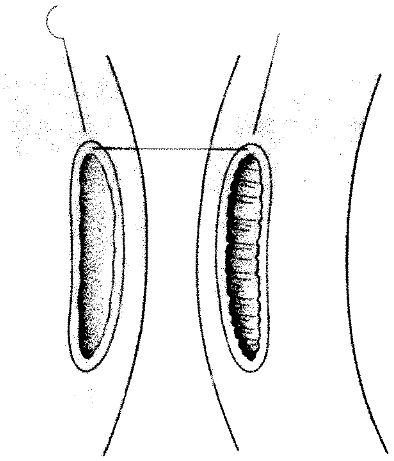

Figure 1 *Start of the anastomosis. The suture is passed through the serosubmucosal layers of the jejunum (on the right) and the stomach (on the left)*

Results

In one patient, who had undergone partial gastrectomy for early gastric carcinoma, anastomotic stricture developed. The stricture required reoperation for persistent vomiting 3 months after the original procedure. There were no wound infections

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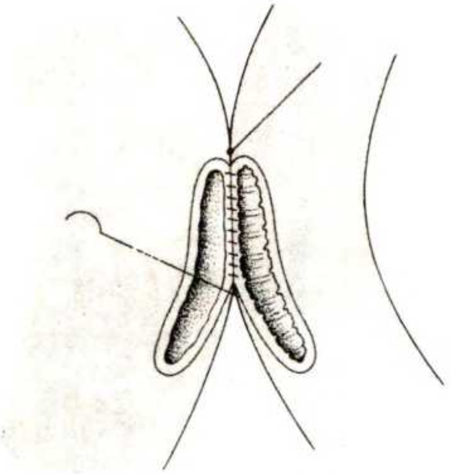

Figure 2 *Suturing of the posterior layer of the anastomosis in progress*

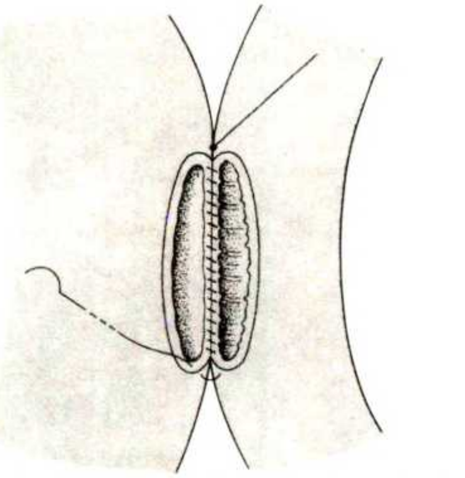

Figure 3 *The posterior layer is complete and the corner is being turned*

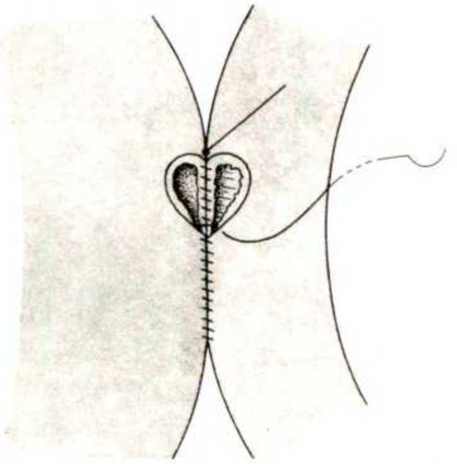

Figure 4 *Suturing of the anterior layer of the anastomosis in progress*

and no other complications related to the anastomosis. One patient died in the immediate postoperative period following gastroenterostomy for inoperable gastric carcinoma. Postmortem examination revealed the cause of death as pulmonary embolism, despite the use of subcutaneous heparin.

Discussion

In an article published in 1887, Halsted[3] was the first to emphasize the importance of the strong submucosal layer of the bowel in anastomotic technique. Based on this observation, Matheson and Irving[4,5] developed the appositional single-layer serosubmucosal method for performing gastrointestinal anastomosis using interrupted sutures[5]. This technique has yielded excellent results and several other authors have confirmed its safety, especially in the large bowel[6-8]. Interrupted sutures have the practical advantage of allowing very accurate matching of bowel ends and the more theoretical advantage of minimizing ischaemia. However, when access is good and the anastomosis technically straightforward, a continuous suture technique is less time consuming, especially when theatre staff are not familiar with the interrupted method.

Single-layer continuous suturing for anastomosis has been described by Sarin and Lightwood[9], who reported leakage rates of 4·5 and 6·2 per cent for the upper and lower gastrointestinal tracts respectively. In their technique all coats of the bowel wall were incorporated in the suture line, but this is neither necessary nor particularly desirable. If only the serosubmucosal layer is employed, the risk of mucosal protrusion is minimized and more precise apposition of the cut edges is feasible.

Fears that a purse-string effect might compromise the lumen have proved unfounded; the single case of anastomotic stricture after partial gastrectomy in the present series was almost certainly caused by failure to create an adequate gastrostomy in the first instance. It might also be argued that the interrupted method causes less disruption to the blood supply and, in demanding situations such as those presented by large bowel or oesophageal resection, continuous suturing is still considered inappropriate. In small bowel, ileocolic and bilioenteric anastomoses, in which mismatching of the cut ends can be a problem, the interrupted technique may also be technically more satisfactory. However, in many situations in the upper gastrointestinal tract, where blood supply and access are not major concerns, continuous single-layer serosubmucosal anastomosis has proved highly satisfactory.

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Resection-line involvement in gastric cancer: a continuing problem

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Surgeons are aware of the adverse effect that resection-line disease has on anastomotic leakage, perioperative mortality and long-term survival. In an attempt to assess the effect of this knowledge on surgical practice, patients entered into the second British Stomach Cancer Group adjuvant therapy trial were studied. The presence of resection-line disease was compared with the operative stage. Of 555 patients for whom complete data were available, resection-line disease was present in 105 (19 per cent). Of 424 patients undergoing what the surgeon considered to be a potentially curative operation, 55 (13 per cent) had involvement of one or both resection lines, rendering the surgery palliative. Only 9 per cent of patients with stage I–III disease and resection-line involvement survived beyond 5 years, compared with 27 per cent of those with clear lines. Despite knowledge of the adverse effects of resection-line disease, surgeons continue to perform inadequate resections. This demonstrates the need for a more aggressive approach to assessment of resection margins at operation.

The aim of surgery in the treatment of solid malignancy is to obtain local clearance whenever possible. At present, only 20 per cent of the 10000 cases of gastric cancer diagnosed annually in the UK are suitable for such a radical approach[1]. However, as interest in early detection increases, this proportion is likely to rise[2]. Resection-line involvement has been shown to have an adverse effect on both anastomotic leakage and mortality[3]. The presence of resection-line disease renders a potentially curative operation palliative[4]. As a result, the long-term survival rate is impaired, with a reduction of over 20 per cent[5] at 5 years. While a number of methods have been suggested to achieve adequate clearance[6,7], most surgeons rely on clinical judgement at operation to decide on the extent of resection. This study looked at the value of this approach to determine whether it provides satisfactory results or whether a more aggressive policy of assessment of resection lines would be beneficial.

Patients and methods

Surgeons referring patients to the second British Stomach Cancer Group trial of adjuvant therapy in gastric cancer were asked to record details of the site and extent of tumour, and the surgery they performed, in a manner similar to that recommended by the Japanese Research Society for Gastric Cancer[7]. Information was requested on serosal involvement, lymph node involvement (and to which group the involved nodes belonged), whether there was ascites or metastatic spread, and whether macroscopic clearance had been achieved. This information has been used to provide an operative stage for the patients using the system outlined in *Table 1*, which is based on the protocol staging system.

Pathological data were collected on serosal and resection-line involvement. Pathologists were also asked to record the number and site of nodes examined as well as whether they contained metastases. All initial pathological assessment was undertaken at the referring hospital and a central review of representative blocks performed by Professor D. Levinson (Guy's Hospital, London, UK). The review blocks did not always include resection margins. Therefore, the resection-margin assessment used is that reported by the pathologist from the referring centre. The presence of serosal or nodal involvement and the surgeon's assessment of clearance have been used to provide a simplified pathological stage using the system in *Table 1*. Both operative and simplified pathological stage have been used to look at the incidence of inadequate surgery as assessed by resection-line involvement.

Table 1 *Simplified system for operative and pathological staging*

Stage	Serosal involvement	Lymph node involvement	Macroscopic clearance
I	−	−	+
II	+	−	+
III	±	+	+
IV	±	±	−

Patients were entered into the study if they fulfilled the entry criteria, which have been detailed previously[1]. The basic criteria were that the patient had stage II–IVAi gastric cancer, was under 75 years of age, had survived the perioperative period and was fit to receive adjuvant therapy. In addition to the trial patients, data were also recorded on patients with stage I disease who failed to fulfil one or more of the entry criteria or where only a completed pathology form was available. Where appropriate, patients have been followed in specialist clinics to death or for a minimum of 5 years.

Data were stored on a minicomputer at the Cancer Research Campaign Trials Unit and analysis undertaken using BMDP Statistical Software (BMDP, Los Angeles, California, USA)[8]. This allowed restaging of patients using the simplified system and cross-tabulation between surgical and pathological data. Pearson's χ^2 test was used to detect any associations in the categorical data.

Survival was the primary endpoint of the study. All patients had a minimum follow-up of 5 years. Survival curves were drawn by the method of Kaplan and Meier, and differences between curves assessed using the log rank test. Stratified log rank analysis was undertaken for patients with disease of pathological stage I–III to determine the impact of resection-line involvement on survival in those undergoing otherwise potentially curative resection. The log rank trend statistic was computed to test whether patients with resection-line involvement in stages I–III had significantly adverse survival than those without involvement. Patients with stage IVA disease were included in the analysis as a separate group for comparison.

Results

Complete surgical and pathological data were available for 555 of the 639 patients referred. The remaining patients were excluded because data were missing for one or more of the staging criteria and in six because of missing follow-up data.

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Table 2 *Relationship between operative stage and involvement of resection margins*

Resection-line involvement	Operative stage I		II		III		IVA	
Upper margin	4	(11)	10	(12)	21	(14)	25	(38)
Lower margin	2		3		9		13	
Both margins	1		0		5		12	
All clear	58	(89)	95	(88)	216	(86)	81	(62)
Total	65	(100)	108	(100)	251	(100)	131	(100)

Values in parentheses are percentages

Table 3 *Relationship between simplified pathological stage and involvement of resection margins*

Resection-line involvement	Pathological stage I		II		III		IVA	
Upper margin	1	(4)	7	(15)	27	(14)	25	(38)
Lower margin	1		5		8		13	
Both margins	0		1		5		12	
All clear	49	(96)	76	(85)	244	(86)	81	(62)
Total	51	(100)	89	(100)	284	(100)	131	(100)

Values in parentheses are percentages

Table 4 *Relationship between type of operation and involvement of resection margins*

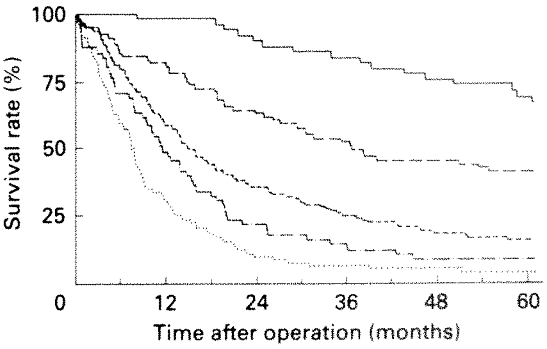
Resection-line involvement	Type of operation*: Distal partial gastrectomy		Proximal partial gastrectomy		Total gastrectomy	
Upper margin	15	(12)	3	(14)	19	(19)
Lower margin	14		2		0	
Both margins	3		1		5	
All clear	245	(88)	36	(86)	104	(81)
Total	277	(100)	42	(100)	128	(100)

*Excludes ten patients with missing information and 98 who underwent a palliative operation

Table 5 *Effect of resection-line involvement by simplified pathological stage*

Pathological stage	Resection-line involvement	No. of patients ($n = 555$)	Time to 75th, 50th and 25th percentiles of survival (months)†: 75th	50th	25th
I	Clear	49	50·30	—	—
	Involved	2	10·18	10·18	36·16
II	Clear	76	14·74	36·72	—
	Involved	13	10·23	15·41	22·10
III	Clear	244	7·20	15·20	37·26
	Involved	40	4·13	9·53	19·53
IVA*	All	131	3·64	7·74	14·07

*Included for comparison only and not used in calculation of the test statistic. †$\chi^2 = 12{\cdot}24$, 1 d.f., $P = 0{\cdot}0005$ (involved *versus* clear stages I–III, stratified log rank analysis)



No. at risk

	0		12		24		36		48		60
I (−)	49	49	48	48	44	42	41	39	37	36	32
II (−)	76	65	62	55	48	44	38	33	33	31	29
III (−)	244	193	145	108	87	75	62	55	47	42	40
I–III (+)	55	39	27	18	12	10	8	7	5	5	5
IVA (all)	131	78	39	25	13	9	8	7	7	5	5

Figure 1 *Effect of resection-line involvement on survival in patients with gastric cancer of stage I (——), stage II (– – –) and stage III (----) without resection-line involvement (−), stages I–III with resection-line involvement (+) (–·–) and stage IVA (·····).* $\chi^2_{\text{trend}} = 49{\cdot}23$, *1 d.f.,* $P = 0{\cdot}0001$ *(log rank analysis of stages I–III clear* versus *stages I–III involved resection lines* versus *stage IVA)*

In 18 patients a pathology form alone was received, in 37 the pathologist was unable to identify any nodes in the specimen, in one the depth of penetration was not recorded, in ten no resection-margin assessment was undertaken, and in 19 data were missing for one or more operative assessment criteria. The number of lymph nodes assessed per patient ranged from 1 to 36 (median 5). The number of involved nodes ranged from 1 to 24 (median 1). Using the operative staging system, 65 patients had stage I disease, 108 stage II, 251 stage III and 131 stage IVA. One or both resection margins were involved in 105 patients (19 per cent). The proximal margin alone was involved in 60 patients, the distal margin alone in 27 and both in 18. The relationship between operative stage and resection-line involvement is shown in *Table 2*. Not surprisingly, there is a significant trend for early-stage disease to be associated with a smaller percentage of involved resection margins ($\chi^2_{\text{trend}} = 25{\cdot}48$, 1 d.f., $P < 0{\cdot}0001$).

Using the simplified pathological staging system, a significant linear trend was observed ($\chi^2_{\text{trend}} = 30{\cdot}71$, 1 d.f., $P < 0{\cdot}00001$) in the incidence of resection-line disease by pathological stage (*Table 3*). In 11 per cent of patients without nodal involvement and disease confined to the stomach, the sole site of known residual disease was the resection margin.

The site of resection-line disease in patients undergoing potentially curative surgery varied with the type of operation performed ($\chi^2_{\text{trend}} = 3{\cdot}78$, 1 d.f., $P = 0{\cdot}05$). In those undergoing total gastrectomy, the proximal margin alone was involved in 15 per cent of cases, with both margins being involved in 4 per cent. There was no case of involvement of the distal margin alone. For patients undergoing partial gastric resection, the figures were similar with single-line involvement at around 11 per cent. A full breakdown is given in *Table 4*.

Log rank analysis showed that resection-line involvement had a significant adverse effect on survival ($\chi^2 = 52{\cdot}93$, 1 d.f., $P < 0{\cdot}00001$), with 355 deaths in the 450 patients without involved lines compared with 100 deaths in the 105 with involved lines. Across all stages, survival was significantly impaired in patients with involved resection margins. The details are shown in *Table 5*.

Survival for patients with simplified pathological stage I, II and III disease with and without resection-line involvement is shown in *Figure 1*. The curve for stage IVA is included for comparison. Log rank analysis demonstrated a significant trend for patients with involved lines or stage IVA disease to have a poorer survival ($\chi^2_{\text{trend}} = 49{\cdot}23$, 1 d.f., $P < 0{\cdot}0001$). Survival for those with resection-line involvement was similar to that for patients with macroscopic residual disease; only five patients (9 per cent) with resection-line involvement survived to 5 years.

Discussion

Surgical treatment of solid malignancy aims for complete removal of disease whenever possible. The extent to which this goal is achieved is likely to be influenced by the surgeon's perceptions of the prognosis of the disease. The poor overall prognosis for patients with gastric cancer, only 5 per cent[9] surviving to 5 years, plays a part in the nihilistic approach to treatment adopted by many clinicians. However, this figure hides the fact that many patients never undergo surgery. Of those with disease localized to the stomach, the 5-year survival rate following resection[10] is over 35 per cent, this figure rising to over 90 per cent for those with disease confined to the mucosa and submucosa[11].

Although surgeons are not accurate in their assessment of serosal or lymphatic involvement, they can identify a group of patients in whom macroscopic clearance can be achieved. At present, the proportion of patients suitable for such an approach[9] is about 20 per cent but with the growing interest in early detection this figure should increase[2]. Where macroscopic clearance is possible, appropriate radical surgery is essential to provide the best hope of cure. When disease is left at the margins after gastric resection, both operative mortality and survival have been shown to be impaired. The presence of resection-line disease at the margin of oesophageal resection has been shown[3] to increase the anastomotic leakage rate from 7 to 100 per cent and the fatal leakage rate from 3 to 100 per cent. In addition, long-term survival is known to be impaired[5]. Using log rank analysis the presence of resection-line disease was seen to be associated with a 20 per cent reduction in the 5-year survival rate and regression analysis has confirmed that it is an independent prognostic variable[10]. The impact on long-term survival has been confirmed in the present study, with survival similar to that seen in patients with macroscopic residual disease. Only 9 per cent of patients with stage I–III disease and resection-line involvement survived to 5 years, compared with 27 per cent of those with clear lines.

A number of methods have been suggested to avoid leaving disease at the resection margins. In defining the surgery required for absolutely curative gastrectomy, the Japanese demand a 5-cm margin from the edge of the tumour[7], a distance that has been validated by further work from Japan[12]. Gall and Hermanek[6] have suggested that the margin may be defined on the basis of preoperative assessment of the histological type of the tumour. In those considered to have the intestinal type of lesion, a margin of 4 cm is recommended. For the group considered to have the diffuse type, the margin should be 8 cm, which would require total gastrectomy in the majority of patients with the diffuse type of tumour[6]. A national study from Norway[13] provided some evidence to support this approach. The incidence of proximal resection-line involvement in those with diffuse tumours was 21 per cent compared with 9 per cent for intestinal tumours[13]. However, this approach, while supported by a historical comparison, lacks prospective confirmation[6]. A third method of deciding on the extent of resection is to undertake intraoperative assessment of the margins by either cytological or frozen-section examination[3]. In addition to routine frozen-section assessment, the use of immunocytochemistry with specific monoclonal antibodies to schirrous carcinoma has been reported to increase the sensitivity of the technique[14]. Although it has been shown to be accurate and is generally available, frozen-section assessment of resection margins is not widely used.

The adequacy of resection is usually decided on clinical grounds by the surgeon at operation. The results of the present study have shown that surgeons are not good at determining the extent of resection required to achieve microscopic clearance within the stomach. The presence of resection-line disease is unlikely to have a major impact on survival in those undergoing palliative surgery and the approach to the extent of resection in such cases goes some way to explain the very high level of resection-line disease in this group. However, in patients considered by the surgeon to be undergoing surgery for disease confined to the muscularis, the incidence of resection-line involvement was unacceptable at 11 per cent. Even when the pathology data are considered, 15 (11 per cent) of the 140 patients without evidence of lymph node dissemination had the resection margin as the only known site of residual disease. Overall, resection-line involvement was the sole site of residual disease in 55 (13 per cent) of the 424 patients undergoing otherwise potentially curative surgery, rendering their operations palliative.

The present study, because of the timing of referral, was not able to provide data on the effect of involvement of resection margins on perioperative morbidity and mortality, and it is important to recognize that these figures represent the minimum incidence of resection-line involvement. These are the postoperative survivors, and the literature indicates that perioperative mortality is highest among those with resection-line disease[3]. Among these survivors, the adverse effect of resection-line involvement on long-term survival has been confirmed. The median survival time for patients with pathological stage II disease is reduced by over 50 per cent and for stage III disease the reduction is 37 per cent.

Although the adverse effects of resection-line disease have been known for some time, the present study has demonstrated that surgeons still perform inadequate surgery, not only in patients with extensive disease but also in those in whom they feel they have some hope of providing a surgical cure. These results clearly demonstrate the need for a much more aggressive policy towards intraoperative assessment of resection lines if the best outcome is to be offered to patients undergoing surgery for gastric cancer. As a minimum, frozen-section assessment of the resection margins should be routine in all those undergoing potentially curative surgery.

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Vertical banded gastroplasty for the treatment of morbid obesity

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Prospective evaluation of 114 obese patients (96 women, 18 men) undergoing vertical banded gastroplasty over a 5-year period was undertaken. The age range was 17–58 (median 37) years, median weight 119·3 (range 79–216) kg, mean(s.d.) proportion of excess body-weight 104·1(34·9) per cent and median body mass index (BMI) 44·8 (range 33·2–77·7) kg/m^2. Three gastric outlet stoma circumferences were used: 5·5 cm (31 patients), 5·0 cm (28) and 4·75 cm (55). A total of 109 patients (95·6 per cent) were available for follow-up. At 1 year after operation, 54 patients (59 per cent) had lost greater than 50 per cent of excess body-weight. No patient lost less than 25 per cent of excess body-weight, and the median BMI was 32·5 (range 21·3–47·8) kg/m^2. The operative mortality rate was zero, but three patients (2·6 per cent) with gastric leakage required surgical revision. Vertical banded gastroplasty is a relatively safe and simple procedure that produces significant and sustained weight reduction in the majority of morbidly obese patients.

Severe obesity is a serious nutritional disorder associated with physical and psychosocial morbidity and mortality. Surveys suggest that 5 per cent of men and 7·5 per cent of women in Western countries are severely obese[1,2]. Morbid obesity is defined as body-weight twice the ideal (according to average weight for height from the actuarial tables of the Metropolitan Life Insurance Company[3]), 45 kg (100 lb) above ideal weight or a body mass index (BMI = weight/height^2) greater than 39 kg/m^2. It is associated with significantly diminished life expectancy[4,5].

Surgical treatment by intestinal bypass[6] was superseded by gastric bypass in the late 1960s. Roux-en-Y gastric bypass has become the standard with which other procedures are compared, although dumping, and iron, folate and vitamin B_{12} deficiencies are not uncommon complications[7].

More recently, various types of gastroplasty have been described. Vertical banded gastroplasty[8] is currently the most frequently performed procedure for morbid obesity in North America and probably worldwide. The attraction of this operation is its technical simplicity and reduced perioperative morbidity rate compared with gastric bypass[7,9,10]. A recent survey, however, showed that bariatric surgery is still practised by only a minority of surgeons in the UK[11].

This study prospectively evaluated the outcome of obese patients undergoing vertical banded gastroplasty in a district general hospital over a 5-year period.

Patients and methods

Since 1986, 114 consecutive patients (96 women, 18 men; median age 37 (range 17–58) years) have undergone vertical banded gastroplasty. All patients were suffering from chronic severe obesity (duration more than 5 years) and had failed conservative efforts to reduce weight.

The ideal weight for height of patients was determined from the midpoint of adult weight range for height tables obtained from the Metropolitan Life Insurance Company[3]. Before operation the median weight was 119·3 (range 79–216) kg, mean(s.d.) proportion of excess body-weight 104·1(34·9) per cent and median BMI 44·8 (range 33·2–77·7) kg/m^2.

Patients were selected for operation after extensive counselling by a team comprising surgeon, nurse clinician, dietitian and clinical psychologist. Twenty-one patients (18·4 per cent) had a BMI less than 39 kg/m^2 at the time of surgery but had all been morbidly obese at some stage previously and had lost some weight by dietary means. A history of alcohol abuse or past psychiatric disorder was considered an absolute contraindication to surgery.

Subcutaneous heparin and broad-spectrum antibiotic prophylaxis were administered routinely.

Operative details

The operative technique has been described in detail elsewhere[8,12]. The median pouch volume was 20 (range 15–50) ml. Initially, the pouch volume was measured during operation using a volumetric filling technique but once consistency had been established the volume was subsequently estimated. The stoma was supported externally by an encircling 1·5-cm wide band of Marlex (C. R. Bard, Billerica, Massachusetts, USA) or GORE-TEX (W. L. Gore, Woking, UK). Three different stoma band circumferences were used: initially 5·5 cm Marlex (31 patients), then 5·0 cm Marlex (28) and, more recently, 4·75 cm GORE-TEX (55). Cholecystectomy was performed in 20 patients (17·5 per cent) in whom coincidental gallstones were found at laparotomy.

Elective postoperative ventilation was undertaken only in patients whose weight was above 189 kg. Patients were usually discharged on day 5 or 6 after operation.

Under the supervision of the dietitian, all patients received mineral and vitamin supplements, a fluid diet for the first 6 weeks and purèed food for the next 6 weeks. A light solid diet was gradually reintroduced thereafter.

Patients were seen at monthly intervals by the dietitian and nurse counsellor to ensure compliance with the dietary regimen. After the initial postoperative visit, medical follow-up was undertaken at 6 months and then annually. Barium or endoscopic examination was performed if indicated.

Statistical methods

Body-weight was expressed as the percentage above ideal weight (percentage of excess weight) for the following time intervals: 6 months, and 1, 2, 3 and 4 years after surgery. The percentage of excess body-weight lost was derived at each time interval.

Patients whose stoma bands were removed because of septic complications were excluded from subsequent weight loss analysis. Those who underwent revisional surgery for weight gain were excluded from analysis after the second procedure. To compare the three different stoma sizes, the mean percentage of excess body-weight lost at each time interval was calculated for each band size and compared using one-way analysis of variance. The incidence of vomiting within each of the stoma size groups was compared using the χ^2 test.

Presented to the Association of Surgeons of Great Britain and Ireland in Oxford, UK, April 1991

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Results

Five patients failed to attend any follow-up appointments. Of the 109 patients (95·6 per cent) available for follow-up, three were excluded from subsequent weight loss analysis owing to postoperative complications necessitating stoma band removal. Thirteen further patients failed to attend on certain occasions. Follow-up data were available on 95 patients at 6 months, 91 at 1 year, 47 at 2 years, 19 at 3 years and five at 4 years.

Weight loss was most rapid during the first year after surgery, after which it was maintained in the majority. *Table 1* shows the number of patients who lost up to 25, 50, 75, or 100 per cent or greater of excess body-weight at each time interval, as well as the mean percentage of excess weight lost. All patients lost weight initially; 1 year after surgery the median BMI was 32·5 (range 21·3–47·8) kg/m^2 and only 12 patients (11·3 per cent) had a BMI greater than 39 kg/m^2 (i.e. were morbidly obese). Five patients (4·7 per cent) eventually regained weight owing to disruption of the vertical staple line or pouch dilatation.

The percentage of excess body-weight lost with time for each stoma band size is shown in *Figure 1*. During the first year the trend was for greater weight loss in patients with smaller stomas. This difference was statistically significant at 6 months ($P < 0·05$, one-way analysis of variance) but subsequently there was no significant difference in the mean weight loss between the three stoma sizes. The numbers of patients within each stoma size group available for longer term follow-up were, however, small.

Table 1 *Frequency distribution of percentage of excess weight lost after vertical banded gastroplasty*

	No. of patients at each time after surgery				
	6 months	1 year	2 years	3 years	4 years
Total no. at follow-up	95	91	47	19	5
Percentage of excess weight lost					
0–25	2	0	2	0	3
26–50	54	37	14	10	1
51–75	35	37	25	8	1
76–100	4	16	6	1	0
>100	0	1	0	0	0
Mean(s.d.)	48·4(14·1)	58·3(17·5)	54·5(19·4)	52·4(15·7)	46·4(16·3)

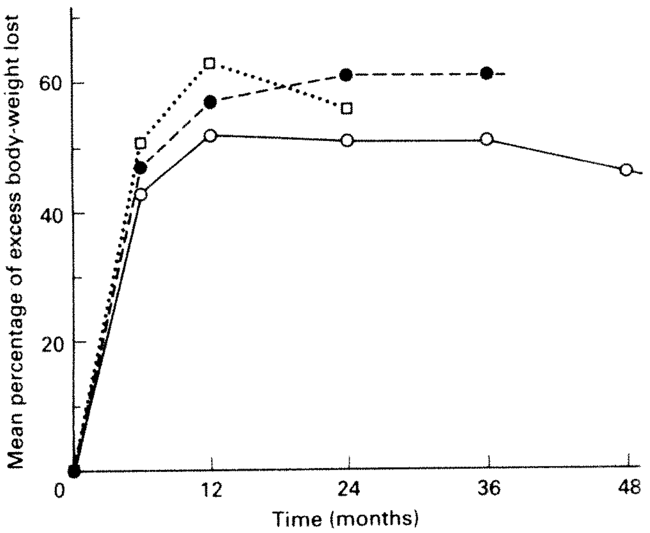

Figure 1 *Mean percentage of excess body-weight lost with time for each gastric stoma band circumference: ○, 5·5 cm; ●, 5·0 cm; □, 4·75 cm. Error bars are omitted for clarity*

Table 2 *Complications following vertical banded gastroplasty*

Complication	No. of patients	Comments
Gastric leakage	3 (2·6)	One patient developed recurrent subphrenic abscesses and a gastric fistula
Respiratory	12 (10·5)	Eight chest infections, three respiratory failures, one respiratory arrest
Wound infection	5 (4·4)	No wound dehiscence
Myocardial infarction	1 (0·9)	
Upper gastrointestinal haemorrhage	1 (0·9)	Severe lower oesophagitis on endoscopy
Vertical staple-line disruption	3 (2·8)*	Regained weight
Pouch dilatation	2 (1·9)*†	Regained weight. Both patients had 5·5-cm bands
Stomal stenosis	10 (9·4)*†	Eight patients had 4·75-cm bands, one had a 5·0-cm and one a 5·5-cm band
Persistent vomiting	2 (1·9)*†	Both patients had 4·75-cm bands but no endoscopic evidence of stomal stenosis. One revised, one lost to follow-up
Bolus obstruction	1 (0·9)*†	Plum-stone retrieved at endoscopy

Values in parentheses are percentages of total number of patients. *Percentage based on number available for follow-up; †percentage excludes those without stoma bands

In addition to maintained weight loss, other less objective parameters of success were documented in many patients, such as employment of those previously without jobs and pregnancy in women who were previously infertile.

Complications

Table 2 shows the incidence of complications. There were no deaths. Because patients with leakage from the gastric staple line required further laparotomy and removal of the stoma band, they were excluded from subsequent weight loss analysis. Of the three patients with disruption of the vertical staple line, two started to regain weight concomitant with the ability to eat normally. One patient reported an ability to eat normally despite satisfactory weight loss. One patient has subsequently declined further follow-up or treatment, another has undergone successful revision by reinsertion of the vertical staple line at laparotomy, and the third is awaiting revision.

Both patients with dilatation of the proximal gastric pouch are awaiting revisional procedures.

One patient with a 5·5-cm band regained weight after 3 years despite initially satisfactory weight loss. This patient declined further investigation, follow-up or treatment and the cause of weight increase is therefore unknown.

The majority of patients with stomal stenosis presented with persistent vomiting between 3 and 16 months after surgery. These patients were treated successfully by endoscopic dilatation. One patient with persistent vomiting despite no evidence of stomal stenosis underwent successful surgical revision by exchange of her 4·75-cm band for one of 5·0 cm. The greater incidence of stomal stenosis and vomiting in the group with 4·75-cm outlets compared with that in the 5·0- and 5·5-cm groups was significant ($\chi^2 = 6·61$, 2 d.f., $P < 0·05$).

Discussion

Weight loss following vertical banded gastroplasty in the present study compares favourably with that reported by others[12–16], although the number of patients reaching longer term follow-up is limited. In patients followed for 5 years or more, Mason *et al.*[17] reported a mean excess weight loss of

58 per cent, suggesting that vertical banded gastroplasty can achieve long-term weight reduction.

In a small proportion of patients failure to lose weight may be due to staple dehiscence or stoma–pouch dilatation[13,18,19]. The principal cause of failure to lose weight is non-compliance with postoperative dietary advice. Careful patient selection and continued emotional support and long-term dietary advice are required.

The relative safety of the procedure is borne out by this and other studies[12–16,18,19]. An operative mortality rate of 0·3 to 0·4 per cent has been reported[20,21]. The most serious complication is gastric leakage, which is fortunately rare, occurring in 0·8 per cent of primary operations[13,21,22]. In the present study there were three gastric leaks (2·6 per cent), with serious consequences in one. This complication may be reduced in incidence or avoided altogether by serosal reinforcement of the circular staple window and covering with omentum, as well as routine testing of the pouch and staple lines by instillation of methylene blue during operation[12].

The optimal pouch volume[12,17,23] is probably 15–30 ml, although there is little in the way of objective evidence to support this. Various methods of measuring pouch volume have been described[23]. Surgeons unfamiliar with the technique of vertical banded gastroplasty should measure volumes until consistency is achieved. Evidence suggests that the stoma of 5·5-cm circumference is associated with significantly less weight loss and more long-term failures, and should no longer be used[12,17]. Very small stoma sizes (under 4·5 cm) may, however, result in inadequate weight loss and a high incidence of vertical staple-line dehiscence[16]. An outlet circumference of 4·75–5·0 cm is probably ideal, although in the present study there was a higher incidence of vomiting in the 4·75-cm group.

All patients with stomal stenosis were successfully managed by endoscopic dilatation. With one exception all patients who required dilatation had Gore-Tex bands, which produce far less tissue reaction and fibrosis than those made from Marlex.

Several studies have compared vertical banded gastroplasty with gastric bypass[7,10,24]. Roux-en-Y gastric bypass is superior to vertical banded gastroplasty in terms of weight loss, but gastric bypass is usually more effective in 'sweet eaters' owing to unpleasant dumping symptoms[10,24]. If patients with a particularly high dietary intake of sweets are excluded, Roux-en-Y bypass results in about 10 per cent more excess weight lost than vertical banded gastroplasty, but at the expense of more postoperative complications[7,10,24]. Others have shown[25,26] that, with close dietary supervision, malnutrition does not occur following vertical banded gastroplasty.

Vertical banded gastroplasty is a safe and relatively simple operation that results in worthwhile and sustained weight reduction in the majority of morbidly obese patients.

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Comparative audit: fact *versus* fantasy

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Comparison of the quality of surgical care has often proved to be an enigma. It still remains more in the realms of fantasy than fact. On the other hand, the quantity of surgical care is fairly easy to determine, audit and compare. Waiting and turnover times, numbers of patients seen and operated on, and the financial cost of surgical intervention can all be measured. Many non-surgeons have used such figures to equate with surgical quality, but this should clearly not be done. Quality is a much more difficult determinant to measure, and the outcome of surgical endeavours must be taken into consideration if anomalies are to be avoided. This fact is exemplified by the surgeon with a 100 per cent perioperative mortality rate. Surgery in this case will be cheap, the turnover rate rapid and waiting time short (no follow-up being necessary), but the quality will be non-existent.

How then can one attempt to define quality? Although many complex definitions are possible, the patient and surgeon each has a simple question to ask. The patient will want to know: 'How good is a surgeon or unit?'. The surgeon will ask: 'How am I performing?'. To address these questions, the possible outcomes of a surgical operation must be determined. The most easily identifiable outcomes are death and complication, and it is not surprising that rates of mortality and morbidity are chosen most often as quality measures. These parameters can be approached using a variety of methods.

Mortality and morbidity meetings form the mainstay of methods used to estimate surgical quality and are the basis of audit in both Europe and the USA. While of obvious benefit, there are three basic difficulties in such an approach. The first is a dichotomy inherent to all audit. On the one hand improvement depends on learning from information about performance, but on the other the same information can easily be used to make and enforce judgements that provoke fear and prevent learning[1]. It is this dilemma that produces most anger and fear among surgeons and remains a major obstacle to the advancement of comparative audit. The second problem with mortality and morbidity meetings is that discussion of a particular death or complication often takes place without reference to whether such an outcome could have been expected. Peer review and hindsight are not always good predictors, even after the effect of bias has been excluded. Third, such meetings exclude discussion of the surgical success: the patient in whom death or complication could have been expected but did not occur. Theoretically such cases have as much, if not more, to teach us as those in which a poor outcome could have been expected.

Unit performance can be compared with published rates for mortality and morbidity in similar units. In this regard a lead has been taken by the Confidential Comparative Audit Service of The Royal College of Surgeons of England[2]. This service allows comparison to be made of workload and resources, but quality issues are more difficult to extrapolate. In 147 882 general surgical admissions reported by Dunn and Fowler[3], the mortality rate varied from 0 to 5 per cent (mean 1 per cent) and the morbidity rate from 0 to 23 per cent (mean 6 per cent). Does this imply that the unit with a 5 per cent mortality rate is worse than one with a rate of 0 per cent? Such an approach has certainly been used to compare cardiothoracic units in the USA. Comparison between units in operative mortality rate following coronary artery bypass grafting has been used in some areas[4,5] to assess quality. Reaction to such 'raw' mortality data by the public and some of the medical profession has led to the closure of units and the discontinuation of programmes. The effect that such data could have on litigation has yet to be quantified. It is of no surprise that differences in outcome occur between units; indeed, such variation is to be expected[6]. It is essential, however, if practice variations are to be assessed, that differences in case-mix are considered.

The recent development of quality-assurance guidelines may induce similar problems, unless used with caution. Certainly one danger of large databases is that mortality and morbidity standards could be set that misrepresent the units with the highest and lowest rates. Although such methods may be helpful in highlighting the need for audit enquiry, they are not reliable enough to allow comparative audit. In an attempt to avoid these difficulties, various groups have devised techniques for producing risk-adjusted mortality and morbidity rates. These methods of quality analysis depend on ability to predict outcome. This objective can be achieved in three ways: scoring systems, regression analysis or a combination of both. Using such techniques, risk-adjusted mortality assessments have been devised for cardiothoracic[7] and general[8] surgery. In the general surgical setting, the POSSUM (Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity) system has the added advantage of producing a risk-adjusted assessment for morbidity as well as for mortality.

These techniques compare data from individual units with a concurrent established database to produce a corrected mortality rate[7] or an observed:expected ratio[9]. A ratio of 1·0 indicates that a unit is performing operations to a quality equal to the mean. A rate of less than 1·0 indicates a performance better than that expected and a value greater than 1·0 worse than expected. These ratios have an obvious practical advantage over 'raw' mortality and morbidity data and allow comparative audit to be contemplated. In the general surgical setting even major differences in case-mix can be accounted for using the POSSUM system[9].

The major danger with all comparative audit data is, of course, their potential for misuse. In the USA this potential has been realized with the publication of uncorrected mortality and morbidity rates, and their use for both overt and covert advertising. Similar problems are beginning to appear in the UK[10]. Risk-adjusted outcome measures could potentially avoid some of these abuses. As yet, such an approach has been developed only for cardiac[7,11,12] and general[8] surgery. In the USA, controlling bodies and groups of surgeons use these differences in risk-adjusted mortality rate between units to assess site visits, so as to examine possible variation in systems and processes. Such an approach has two major advantages over existing audit methods. Examination of 'good' units should highlight potentially better surgical technique and practice, which could be of benefit to all. Examination of the poorer performing units may highlight deficiencies known to these that, because of other influences such as financial constraints and staffing levels, they are not able, unaided, to correct. In the latter instance, the full weight of medical audit opinion may produce the necessary improvement. We should not be afraid to find deficiencies in surgeons and to approach these in the same way.

If surgeons are to improve the quality of work, we must be brave enough to assess our own performance and compare it with that of others. If deficiencies are found, we must be both prepared and allowed to examine the systems that surround us

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and the methods adopted. Such analyses will take time and resources, and surgeons need to be more forthcoming with the results of their audit deliberations if this investment is not to be wasted. It is essential in this regard, if improvement is to be attempted, that there is trust and patience between clinicians and managers.

Can comparative audit become more than fantasy? The Royal College of Surgeons has taken a lead at a national level, but with the development of risk-adjusted outcome analysis the methodology exists to examine quality in a more systematic way on a local as well as national scale. Comparative audit can become fact, but we must have the courage to embrace it. It should never be forgotten, as eloquently stated by Berwick[1], that, as well as the auditor's courage, others must show the wisdom of restraint if continuous quality-improvement is to follow from comparative audit.

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Reoperation for biliary tract complications following orthotopic liver transplantation

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Biliary tract complications were analysed after 54 orthotopic liver transplantations performed in 49 patients over a 2-year period. Reconstruction of the bile duct consisted of end-to-end choledochocholedochostomy over a T *tube in 47 cases and Roux-en-*Y *choledochojejunostomy in seven (two for sclerosing cholangitis, one for secondary biliary cirrhosis, four retransplants). The* T *tube was withdrawn 12–16 weeks after operation in all but two patients (2–3 weeks). There was no intraoperative mortality. Eight patients (16 per cent) died during the first month and the 1-year actuarial survival rate was 75 per cent. Early biliary complications (up to 3 months after operation) consisted of five bilomas, for which ultrasonographically guided drainage was effective in three and surgical drainage necessary in two. Late biliary complications (3 months onwards) consisted of biliary peritonitis following* T *tube removal (four patients; reoperation was required in all four) and necrosis of the bile duct secondary to a late arterial thrombosis (one). The incidence of reoperation as a result of early biliary complications was low (two patients), but higher for biliary peritonitis following* T *tube removal.*

Despite technical improvements in orthotopic liver transplantation (OLT), biliary complications are still a frequent cause of postoperative morbidity[1–5]. The incidence of less than 10 per cent reported recently[2,6] is far removed from the 34–50 per cent noted in 1977 by Starzl *et al.*[7] and Calne and colleagues[8]; most publications[1,4,5,9–12] show an incidence of 10–34 per cent. The aim of the present study was to analyse biliary tract complications after the first 54 liver transplantations performed in this hospital.

Patients and methods

Over a 2·5-year period, a total of 54 OLTs were performed in 49 patients (30 male, 19 female) aged between 10 and 63 years. Indications for transplantation are listed in *Table 1*.

For the first eight grafts, EuroCollins solution was used as a preservation fluid; for the remaining 46, University of Wisconsin solution was employed. The mean(s.d.) cold ischaemia time for the donor liver was 405(104) (range 180–700) min. In 15 cases (28 per cent) haemodynamic intolerance to clamping of the inferior vena cava and portal vein led to the use of venovenous bypass. The mean(s.d.) time for surgery on the recipient was 479(113) (range 280–705) min.

All the liver removals from the donor and implants in the recipient were performed using the technique described by Lerut *et al.*[3] and Calne[13]. Reconstruction of the biliary tract consisted of end-to-end choledochocholedochostomy in 47 cases and Roux-en-Y choledochojejunostomy in seven (two for sclerosing cholangitis, four retransplants, one for secondary biliary cirrhosis). Choledochocholedochal anastomosis was performed with a single layer of interrupted 4/0 resorbable suture (polyglactin); a T tube was left in the bile duct and the long limb brought out through a small incision in the recipient duct, at least 1 cm from the divided end. Choledochojejunal anastomosis was also performed with a single layer of interrupted 4/0 polyglactin, and a multiperforated stenting cannula left in the anastomosis. The stent was pulled through after being fixed to the jejunal loop using Witzel tunnelation. All patients with a choledochocholedochostomy underwent routine intraoperative cholangiography after reconstruction. The T tube and stent were removed after 12–16 weeks, except in one patient whose T tube was accidentally dislodged in the third week (without biliary complications) and in another with a choledochojejunostomy, whose stent was removed early (week 2) after a severe episode of cholangitis; no biliary tract complications were observed in this patient and the cholangitis subsided.

Table 1 *Indications for 54 orthotopic liver transplantations*

	No.
Hepatic cirrhosis	
Alcoholic	15*
Postnecrotic	12*
Cryptogenic	1
Primary biliary	1
Secondary biliary	1
Total	30
Fulminant hepatitis	10
Other causes	
Wilson's disease	2
Hepatoma without cirrhosis	2
Sclerosing cholangitis	2
Budd–Chiari syndrome	1
Familial amyloidosis	1
Giant adenoma	1
Total	9
Retransplants	
Arterial thrombosis	1
Portal ischaemia	1
Primary dysfunction	1
Chronic rejection	1
Uncontrollable acute rejection	1
Total	5

*One with hepatocellular carcinoma

Biliary complications were considered as early if the onset was before the third month after operation and as late if after this time. Survival was analysed using the P1L program of the BMDP package (BMDP Statistical Software, Cork, Ireland), and the curve and probability of survival in patients undergoing transplant were obtained by actuarial methods[14].

Results

Mortality

There was no intraoperative death. Eight patients (16 per cent) died in the first month after operation (*Table 2*). In the second

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Table 2 *Causes of death in the first month after operation*

	No. of patients	Survival (days)
Sepsis (bronchopneumonia)	3	10, 20, 23†
Sepsis (mycosis)	1	25
Cerebral bleeding	1	2
Arterial thrombosis	1*	3
Primary graft dysfunction	1*	3
Ruptured pseudoaneurysm	1	18†

*Died awaiting retransplant; †days after retransplantation

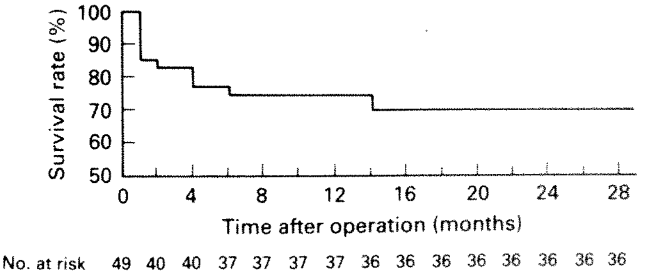

Figure 1 *Actuarial survival in 49 patients undergoing orthotopic liver transplantation*

Table 3 *Biliary tract complications*

	Time after surgery (months)	Type of anastomosis	Treatment	Comments	Outcome
Early					
Biloma	2	Choledochocholedochostomy	Drainage	—	Recovered
Biloma	1	Choledochocholedochostomy	Drainage	—	Recovered
Biloma	1	Roux-en-Y	Drainage	—	Recovered
Biloma*	1	Roux-en-Y	Drainage	T tube dislodgement	Recovered
Biloma*	1	Roux-en-Y	Drainage	T tube dislodgement	Recovered
Late					
Biliary peritonitis†	4	Choledochocholedochostomy	Reoperation	Silicone tube	Recovered
Biliary peritonitis†	4	Choledochocholedochostomy	Reoperation	Latex tube	Recovered
Biliary peritonitis†	3	Choledochocholedochostomy	Reoperation	Latex tube	Recovered
Biliary peritonitis†	4	Choledochocholedochostomy	Reoperation	Silicone tube	Recovered
Bile duct necrosis	3	Choledochocholedochostomy	Reoperation	Arterial thrombosis	Died

*Septic; †following T tube removal

month, two patients died, both from sepsis and multiorgan failure: one infection was intra-abdominal (infected haematoma) and the other of pulmonary origin. Between 3 and 12 months a further two patients died, one from sepsis of pulmonary origin and the other from acute uncontrolled rejection while awaiting retransplantation. Finally, after 1 year, one patient died from pulmonary metastasis after a recurrence of hepatoma. The actuarial survival rate of the 49 patients receiving 54 OLTs was 75 per cent at 12 months and 70 per cent at 28 months (*Figure 1*).

Biliary tract complications

Complications occurred in ten cases (19 per cent) and six needed surgical treatment.

Early biliary tract complications (before the third month) occurred in five cases (9 per cent) (*Table 3*). All presented with a bile collection in the subhepatic space (biloma); one was associated with an external bile fistula around the T tube. Three of the patients had symptoms of cholestasis and high levels of bilirubin and alkaline phosphatase, and two presented with fever with pain and muscle guarding in the right hypochondrium. Ultrasonography in all cases disclosed a collection of subhepatic fluid. Cholangiography revealed a bile leak in three patients. In the other two (those with fever and muscle guarding) there was dislodgement of the T tube from the biliary tract. Ultrasonographically guided drainage was attempted in all five patients and proved effective in three; the two failures occurred in those with sepsis and T tube dislodgement, for whom surgery was indicated. In one patient (on day 20 after operation) the T tube was reinserted and a subhepatic drain was left; in the other (on day 25) the T tube was removed and a subhepatic drain left. Both patients progressed without complication.

Late biliary tract complications (from the third month onwards) occurred in four patients who developed diffuse acute peritonitis after T tube removal between 3 and 4 months after surgery. The tube was latex in two cases and silicone in two. All needed an emergency laparotomy within 24–48 h of withdrawal. Abundant peritoneal bile was found in all four patients. The abdominal cavity was lavaged and a subhepatic drainage tube left, which was removed 3–6 days after operation. All four patients progressed satisfactorily.

A further patient was readmitted to hospital 3 months after transplantation (donor liver of an incompatible blood group in a patient with fulminant hepatitis) for symptoms of pruritus and increased levels of transaminase and alkaline phosphatase, but with a normal bilirubin concentration. Cholangiography revealed considerable cavitation at the hepatic hilum. This was confirmed by a liver isotope study, which revealed a number of cavities in both hepatic lobes. Doppler ultrasonography did not show fluid at the hepatic artery. Retransplantation was indicated and surgery revealed hepatic artery thrombosis, necrosis of the whole donor duct and multiple cavities of various sizes in both hepatic lobes. The retransplanted organ developed primary graft dysfunction and further transplantation was needed, this time with arterial reconstruction using anastomosis between the donor thoracic aorta and the recipient infrarenal abdominal aorta. After this second retransplant, the patient developed sudden fulminant signs of hypovolaemic shock (on day 18 after operation) secondary to rupture of an aortic pseudoaneurysm at the arterial anastomosis, and died.

Discussion

Currently, the most commonly used techniques for biliary tract reconstruction in OLT are end-to-end choledochocholedochostomy as a first-choice procedure[1,3,15] and Roux-en-Y choledochojejunostomy in cases where the recipient duct is pathological or there is a clear difference in size with that of the donor[1–3]. However, some workers routinely use other procedures such as the gallbladder conduit[13] or side-to-side choledochocholedochostomy[4,16]. The authors' procedure of choice is end-to-end choledochocholedochostomy[3] and the second option (in cases of sclerosing cholangitis, secondary biliary cirrhosis, retransplant, size difference between donor and recipient ducts) is Roux-en-Y choledochojejunostomy or hepatojejunostomy.

The most frequent biliary tract complications after transplantation are fistula and biliary obstruction[1–5,17,18]. There were no strictures of the anastomosis in the present series; biloma was the commonest complication. Initially, any biloma was treated conservatively with ultrasonographically guided drainage, as advocated in most series[19–21]. Surgery is indicated in two situations: when radiological drainage has not been effective, and when the amount of bile does not tend to decrease with time.

In the present series, the second most frequent complication was fistula with diffuse acute peritonitis following T tube removal. To prevent this complication, some have advocated leaving the T tube in place for longer periods and using tubes made from non-inert materials. This achieves a greater local inflammatory response[22–24], although less so in patients receiving steroids, and enables the formation of a track with well established walls between the bile duct and the exterior, which should prevent diffuse acute peritonitis following withdrawal of the T tube. In the present patients the T tube was left for a minimum of 12 weeks and, when biliary peritonitis developed following tube removal, the tube was silicone in two cases and latex in the other two. One of the patients accidentally dislodged the T tube during the third week after operation, but developed no biliary tract complications. Good results have recently been reported[25] when treating bile leakage after T tube withdrawal with early transpapillary nasobiliary catheter insertion in the course of duodenoscopy.

It should be noted in the present series that more than half of the biliary complications were directly related to the T tube (two bilomas occurred following tube dislodgement from the bile duct and four cases of bile peritonitis followed removal of the tube). To prevent this type of complication, it has recently been suggested[26] (with good results) that a T tube should not be left after performing the end-to-end choledochocholedochostomy. Further studies will be necessary to confirm the efficacy of this procedure.

Necrosis of the bile duct is an infrequent problem associated with arterial thrombosis[18]. One of the present patients developed this complication. Arterial thrombosis in this case may have been related to a hyperacute rejection episode a few days after transplantation, in which the graft was of an incompatible blood group.

In conclusion, although the rate of biliary tract complications following OLT has diminished in recent years, they still represent a frequent postoperative problem. Excluding the four cases of peritonitis following T tube removal and the necrosis of the bile duct secondary to arterial thrombosis, the incidence of biliary tract complications in the present series was minimal (9 per cent), possibly owing to the experience of the surgical team[27,28].

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Native and graft pancreatitis following combined pancreas–renal transplantation

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Ten patients who had undergone whole-organ pancreas transplantation and pancreatoduodenocystostomy from a total of 60 simultaneous cadaveric kidney–pancreas transplants met the criteria for graft pancreatitis. This condition is clearly different from acute rejection on the basis of marked hyperamylasaemia and significant local findings over the allograft. Graft rejection was the cause of graft loss in one of the patients; eight are alive, seven with a functioning graft 61, 30, 27, 25, 21, 18 and 14 months after transplantation. Two patients died: one from severe graft pancreatitis and the other from cytomegalovirus infection. Bladder drainage with or without antibiotics has been the most common therapy, based on the theory that damage is caused by duodenal content and infected urine reflux. To prevent graft loss, antiviral treatment should be given when pancreatitis due to cytomegalovirus is suspected or diagnosed. Two patients with native pancreatitis are also described; the disease was severe and surgery was required in both cases. The pancreas grafts have now been functioning for 2 years 7 months and 2 years 10 months respectively.

According to the International Pancreas Transplant Registry[1] the results of pancreatic graft survival have shown a progressive improvement, comparable to that obtained for transplantation of other solid organs. Failure of a pancreatic allograft can be attributed to immunological or non-immunological causes. Mechanisms of non-immunological graft loss include thrombosis, infection and pancreatitis.

Pancreatitis constitutes an infrequent cause of graft loss[2]. This complication can present early in the postoperative course in association with preservation damage, or late, often occurring months after transplantation. Differentiation between graft pancreatitis and rejection can be difficult in some patients, but graft pancreatitis is clearly distinguishable from acute inflammation of the native pancreas. Acute native pancreatitis is a rare complication after renal transplantation, and can also occur following simultaneous renal–pancreas transplantation.

The purpose of this study was twofold: first, to determine the factors that predispose to late graft pancreatitis to establish the optimal treatment and, second, to document experience of acute native pancreatitis and its management.

Patients and methods

Between February 1983 and July 1992, 60 primary cadaveric simultaneous kidney and pancreas transplants were performed in adults with type I diabetes mellitus. Only one patient had a segmental graft occluded with prolamine. In the other patients, exocrine pancreatic graft secretions were drained to the urinary tract using techniques described previously[3,4]: to the renal pelvis in four patients, to the ureter in five and to the bladder (duodenocystostomy technique) in 50.

There were 45 men and 15 women. The mean age of patients was 36·4 (range 25–51) years. The mean duration of insulin-dependent diabetes mellitus (IDDM) was 20·4 (range 12–33) years. The pancreas was preserved under cold storage conditions with Collins' solution ($n = 24$) and, more recently, with University of Wisconsin solution ($n = 36$). Postoperative immunosuppression consisted of azathioprine and prednisone (five patients), prednisone and cyclosporin (12) or quadruple therapy with cyclosporin, prednisone, azathioprine and prophylactic antilymphoblast globulin (43). Episodes of rejection were treated with pulsed corticosteroids or OKT3.

All patient records were reviewed retrospectively for episodes of abdominal pain associated with hyperamylasaemia. Ten patients (eight men), with a mean(s.d.) age of 39·4(7·6) years and IDDM for a mean(s.d.) of 19·7(5·3) years, had clinical criteria compatible with the definition of allograft pancreatitis: an inflammatory process of the pancreas allograft with rapid onset of symptoms and usually presenting with lower abdominal pain and raised levels of pancreatic enzymes in the blood. The condition is usually associated with stable renal allograft function and minimal organ disturbance. Serum glucose (normal value 80–110 mg/dl), lipase (normal < 200 units/l), amylase (normal < 400 units/l) and urinary amylase levels were determined regularly, and intravenous and oral glucose tolerance tests carried out serially at 1-year or shorter intervals in all patients suspected of graft pancreatitis.

In all patients with clinical suspicion of graft pancreatitis, duplex Doppler ultrasonography was performed. Pancreatic size, echostructure and perigraft–intra-abdominal fluid were evaluated by real-time ultrasonography. A pulsed Doppler study was performed thereafter to assess the permeability of the vascular pedicle at the hilum. Venous and arterial Doppler spectra were also obtained of graft parenchyma (head, body, tail). The arterial pulsed Doppler spectrum was quantified by the resistive index (RI):

$$\mathrm{RI} = \frac{\text{peak systolic velocity} - \text{end diastolic velocity}}{\text{peak systolic velocity}}$$

Three consecutive waveforms were obtained at each parenchymal level and the final RI derived from the mean of these values. Patients were also checked for lower urinary tract infection. Cystography was performed when bladder or duodenal perforation was suspected.

Diagnosis of cytomegalovirus (CMV) infection was performed by CMV serology and/or histological examination. Serological testing for CMV-specific immunoglobulin (Ig) G and IgM antibodies was carried out by complement fixation. Seroconversion for IgG and/or IgM was required for the diagnosis of primary CMV infection. Reactivated infection was diagnosed by an increase in CMV-specific IgG level to four times the previous value. Histological diagnosis of CMV infection was made when a pancreatic graft biopsy showed inclusion bodies in the acinar cells.

Two patients had native acute pancreatitis (acute inflammation of their own pancreas) and are considered separately.

Results

Graft pancreatitis

Ten patients met the criteria for graft pancreatitis. All had undergone whole-organ pancreas transplantation with duodenocystostomy. The total number of episodes was 22 with a mean(s.d.) of 2·2(0·4) (range 1–5) episodes per patient. The

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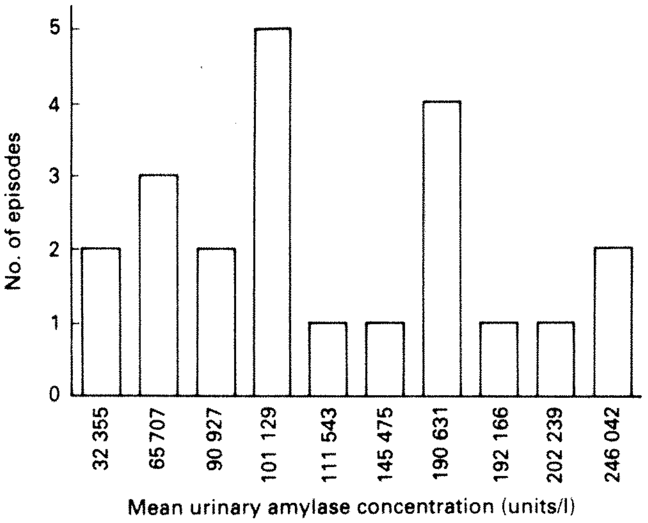

Figure 1 *Relationship between urinary amylase level and number of episodes of pancreatitis for each patient*

mean(s.d.) time of occurrence was 341(76) days after transplantation. Abdominal pain was present in all patients. Other symptoms, such as fever (ten patients), dysuria (eight), haemorrhagic cystitis (one), paralytic ileus (four) and shock (one), were also observed. Physical findings were characterized by tenderness of the lower abdomen (22 episodes), abdominal distension (22) and ascites (one). All patients had marked hyperamylasaemia (mean(s.d.) level 1620(182) units/l) and hyperlipasaemia (mean(s.d.) level 1415(417) units/l). Endocrine graft function remained normal (mean(s.d.) serum glucose level 107(10) mg/dl) in all patients during the episodes of graft pancreatitis.

As shown in *Figure 1*, there was great variability in the mean urinary amylase level of patients with pancreatitis. Those with graft pancreatitis had the same number of rejection episodes (one or two) as those without inflammation of the graft.

Duplex Doppler ultrasonography of normal grafts showed a homogeneous structure without pancreatic duct dilatation (<2 mm), and the graft size did not exceed the expected dimensions of a normal pancreas. On pulsed Doppler examination, the venous spectrum showed continuous flow. Quantification of the arterial Doppler spectrum in stable grafts (>2 months after grafting) showed a mean(s.d.) RI of 0·62(0·01). Results with duplex Doppler ultrasonography in the follow-up of pancreatic grafts and in graft rejection episodes have been partially reported previously[5,6] and are summarized in *Table 1*. The most common abnormalities seen on ultrasonography in graft pancreatitis were perigraft fluid and graft hypoechogenicity. The pulsed Doppler RI could differentiate between graft pancreatitis and rejection (75 per cent sensitivity, 95 per cent specificity). The latter is characterized by a significant increase (mean(s.d.) 0·79(0·14)) compared with the RI value obtained before rejection (0·62(0·05)). However, the RI in graft pancreatitis (0·61(0·04)) is similar to that measured before episodes of pancreatitis (0·63(0·01)).

Twelve episodes were clearly associated with bladder outlet obstruction resulting in urine retention or stasis secondary to a large bladder. Urinary infection was encountered in 19 of 22 episodes of graft pancreatitis (*Staphylococcus epidermidis*, nine patients; group D enterococcus and *Staphylococcus epidermidis*, three; *Pseudomonas* species, six; other Gram-positive organisms, one). Three episodes of CMV graft pancreatitis were documented in two patients: one died from multiple organ failure 2 months after grafting, and pancreatic graft biopsy showed inclusion bodies in acinar cells; the other suffered two episodes of graft pancreatitis during which seroconversion for CMV-specific IgG antibodies (titre 1/128) was detected. By 2 months later these titres were negative but the patient developed irreversible rejection resulting in graft failure.

Indwelling bladder drainage was the most frequent therapy for episodes of graft pancreatitis (22 episodes), and antibiotics were also given when urinary infection was documented (19). Other treatments used were bowel rest (18 episodes), oral pancreas extract (two), somatostatin (three), total parenteral nutrition (one) and anti-CMV therapy (two). Bladder irrigation with saline and the protease inhibitor aprotinin was successfully used in one patient with haemorrhagic cystitis. The mean(s.d.) time for resolution of the hyperamylasaemia and abdominal pain was 7·2(1·8) (range 2–41) days.

Three patients developed local complications. One graft duodenocolic fistula was managed conservatively; there were two bladder fistulas, in one complicated by peritoneal ascites which healed spontaneously; in the other surgical repair was required.

Severe graft pancreatitis associated with organ failure was observed in one patient after conversion of the graft from bladder to intestinal drainage, with cessation of endocrine and exocrine pancreatic function and progressive deterioration leading to death 10 days after conversion.

Eight patients are still alive. Pancreatic graft rejection led to graft failure in one patient. In the other seven, both kidney and pancreas are currently functioning and the patients do not require insulin 61, 30, 27, 25, 21, 18 and 14 months after transplantation.

Native pancreatitis

Patient 1. A 29-year-old man underwent combined cadaveric renal–pancreas transplantation in November 1989. Both grafts functioned immediately after transplantation. Immunosuppression consisted of cyclosporin, azathioprine and prednisone. The pancreas was drained via a duodenocystostomy. Rejection of the kidney and pancreas was treated 1 month after transplantation with pulsed doses of corticosteroids and OKT3, and 6 weeks later with bolus steroids. At 10 days after treatment the patient developed CMV infection with neurological signs of rhomboencephalitis, and was treated with antiviral therapy. Some 4 months after this episode and 6 months after transplantation he presented with repeated episodes of right hypochondrial and epigastric pain for 7 days, followed by sudden collapse. At laparotomy there was peripancreatic and splenic haematoma; splenectomy and peripancreatic debridement were performed. Peripancreatic drains were placed for lavage for 10 days. The postoperative course was uneventful.

This patient is currently well with both kidney and pancreas functioning (insulin-free) for 2 years 7 months.

The exact mechanism of native pancreatitis in this patient is unknown but CMV infection and the previous potent antirejection treatment may have contributed.

Table 1 *Duplex Doppler ultrasonography following pancreas transplantation*

	Graft rejection		Graft pancreatitis	
Real-time ultrasonography*				
Size	Increased	33	Increased	4
Structure	Heterogeneous	33	Heterogeneous	4
	Hypoechoic	12	Hypoechoic	16
Duct of Wirsung	Dilated	4	Dilated	4
Duodenal wall	Increased	4	Normal	100
Perigraft fluid		38		50
Pulsed Doppler ultrasonography				
Mean(s.d.) resistive index				
Before	0·62(0·05)†		0·63(0·01)‡	
During	0·79(0·14)§		0·61(0·04)	

*Values are percentages of patients showing the changes. †$P < 0{\cdot}05$, ‡P not significant (before *versus* during graft rejection, Student's t test); §sensitivity 75 per cent, specificity 95 per cent (graft rejection *versus* pancreatitis)

Patient 2. A 36-year-old man underwent combined renal–pancreas transplantation in January 1990. The pancreas was drained via a duodenocystostomy. Both grafts functioned immediately after transplantation. At 6 months there was rejection of both organs, which was successfully treated with pulsed doses of corticosteroids. Some 3 weeks later the patient experienced an episode of graft pancreatitis and dysuria, managed with a urinary Foley catheter for 3 days. At 12 months after transplantation, renal function deteriorated as a sign of ongoing chronic rejection despite good endocrine and exocrine pancreatic graft function. Haemodialysis was instituted 16 months after transplantation. The patient underwent renal retransplantation 2 years after primary transplantation and the kidney graft was placed in an orthotopic position. The graft functioned immediately, with no change in the triple immunosuppression therapy. However, 2 weeks later he developed abdominal pain with a marked rise in the serum amylase level (mean 1142 (range 1059–1237) units/l) and clinical evidence of sepsis. Endocrine pancreatic graft function remained normal.

Ultrasonography showed that both kidney and pancreas grafts were of normal size. However, a fluid collection was detected near the head of the native pancreas in the subhepatic region. Percutaneous, then surgical, drainage revealed 300 ml pus containing group D enterococcus and *Pseudomonas* species. Some 6 weeks later a 6-cm pseudocyst was detected in the body of the pancreas. Cystogastrostomy was performed with complete resolution of the clinical symptoms. This patient has to date had both kidney and pancreas functioning (insulin-free) for 2 years 10 months.

The native pancreatitis in this case may have been related to intraoperative injury to the gland at the time of kidney graft placement in the orthotopic position.

Discussion

Graft pancreatitis can be differentiated from acute rejection on the basis of marked hyperamylasaemia and significant local findings over the allograft, both of which are not characteristic of acute rejection. Stratta *et al.*[7] have reported that only 17·7 per cent of rejection episodes are associated with hyperamylasaemia. In the present group of ten patients, eight had had nine previous rejection episodes but hyperamylasaemia was observed in only one episode. Furthermore, endocrine pancreatic function was not affected; all the patients maintained normoglycaemia and good exocrine function with little or no modification of urinary amylase levels from the baseline. In addition, the absence of changes in renal function over time and the improvement in hyperamylasaemia without changes in immunosuppressive therapy are against isolated pancreatic rejection.

No correlation was observed between levels of urinary amylase and the frequency of episodes of graft pancreatitis, showing that the amount of exocrine secretion is not predictive of the occurrence of inflammatory responses in the graft. Patients without graft pancreatitis with stable functioning grafts also show great variability in the level of urinary amylase. However, urinary amylase monitoring is reliable[8,9] in the diagnosis of graft rejection when the level of urinary amylase in an individual patient falls by 50 per cent.

Late graft pancreatitis was thought to be unique to the bladder drainage technique but it has been associated with enteric diversion[10]. Stratta *et al.*[7] reported 43 episodes in 19 patients with bladder drainage. Concomitant urinary tract infection was documented in 64 per cent of patients and short-term Foley catheter drainage plus antibiotic therapy successfully reversed 39 of the 43 episodes. See and Smith[11] demonstrated that active proteolytic enzymes are present in the urine of many patients with a duodenocystostomy. These observations may be related to the mechanisms of graft pancreatitis. Urinary retention and stasis facilitate the activation of proteolytic enzymes, which leads to the breakdown of the normal bladder and duodenal mucosal barrier and facilitates colonization by bacteria. The reflux of bladder–duodenal content with active trypsin and infected urine may damage the ductal mucosal barrier, resulting in intrapancreatic activation of enzymes[12]. Another possibility could be increased pressure in the pancreatic duct secondary to the increased pressure in the bladder associated with urethral or bladder obstruction. It is noteworthy that bladder drainage with or without antibiotics resulted in resolution of the majority of episodes of pancreatitis; however, recurrent episodes were common. Another explanation could be occlusion of the sphincter of Oddi secondary to rejection. This process could cause ductal occlusion as a result of local mucosal swelling, impaired blood flow and necrosis leading to ductal stenosis. In a series of 124 pancreatic grafts, Backman *et al.*[13] reported eight patients with pancreatitis associated with ongoing CMV infection; five developed intrapancreatic abscesses and four of the grafts were lost. To prevent graft loss, antiviral treatment should be given when CMV pancreatitis is suspected or diagnosed[14].

The occurrence of graft pancreatitis does not lead to graft loss. Of ten of the present patients, seven still retain a functioning graft. Graft rejection led to graft loss in one patient. Two patients died, one from severe graft pancreatitis and one from CMV infection.

Acute pancreatitis is an infrequent but severe complication of renal transplantation[15]. A number of aetiological factors may contribute to pancreatitis. Possible explanations for the development of native pancreatitis following combined renal–pancreas transplantation and renal transplantation alone are the intensive immunosuppressive regimen used, the development of CMV infection and pancreatic injury in cases of orthotopic renal transplantation using the splenic vessels of the recipient for revascularization. The differential diagnosis between native and graft pancreatitis is usually not difficult. Graft pancreatitis is frequently associated with fever, graft tenderness, lower abdominal pain and abdominal distension. In native pancreatitis the physical findings are upper abdominal pain and the systemic manifestations are more severe.

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Case report

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Intestinal obstruction following laparoscopic inguinal hernia repair

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Following the success of laparoscopic cholecystectomy, the list of procedures that have been attempted laparoscopically is expanding rapidly[1]. For laparoscopic inguinal herniorrhaphy the goal is to reduce the recurrence rate, decrease postoperative morbidity and reduce the time off work compared with the open operation. The complications associated with this new technique are at present unclear, but should now include intestinal obstruction.

Case report

A 20-year-old man was admitted for repair of a right inguinal hernia. Laparoscopic preperitoneal mesh herniorrhaphy was performed. After transverse incision of the peritoneum above the hernial defect and dissection of the preperitoneal space, the sac was reduced and a Marlex mesh (C. R. Bard, Billerica, Massachusetts, USA) cut to the required size and fixed into place with staples. Peritoneal closure over the repair was by staples and sutures; the total operating time was 60 min. The patient made an uncomplicated recovery and was discharged home the next morning.

Some 4 days after operation the patient was readmitted with a 1-day history of colicky central abdominal pain, vomiting and constipation. He also complained of pain in the right groin radiating to the upper medial thigh. On examination the man had mild abdominal distension, obstructive bowel sounds and tenderness over the right iliac fossa. Plain radiography confirmed the impression of small bowel obstruction. The patient was treated conservatively by nasogastric aspiration and intravenous fluid administration. The intestinal obstruction and groin pain settled, and 4 days later he went home.

The patient was readmitted 7 days later with the same clinical and radiological picture of small bowel obstruction with reduced pin-prick sensation in the upper medial aspect of the right thigh. After rehydration, laparotomy revealed that the peritoneal repair covering the mesh had separated at its lateral extent. A loop of distal ileum had herniated through the defect, was adherent to the Marlex mesh and obstructed at this point. Gentle blunt dissection freed the adherent obstructed segment of distal ileum and, apart from repair of the peritoneal defect, no further procedure was required. The postoperative recovery was uneventful; the patient was discharged home 6 days after operation and 1 month later was asymptomatic.

Discussion

This paper describes a predictable and major complication following laparoscopic preperitoneal mesh repair of an inguinal hernia. The cause of failure of the peritoneal repair over the mesh is unclear, but probably related to a tight repair with failure of the staples and sutures to hold the peritoneum, thus allowing adherence of small bowel to the mesh.

An intraperitoneal onlay mesh technique of laparoscopic herniorrhaphy has recently been described[2]. There are obvious concerns regarding this method because of the possibility of bowel adherence to the uncovered mesh. The pain and diminished sensation in the right thigh of the present patient were probably related to oedema around the femoral branch of the genitofemoral nerve rather than to stapling of the nerve since symptoms settled after laparotomy.

A recent review of laparoscopic hernia repair in several centres[3] reported a complication rate of less than 10 per cent including anterior thigh and testicular pain, haematoma formation and bladder injury; the short-term recurrence rate was low (under 0·8 per cent). No other case reports describing the complication encountered here, following laparoscopic preperitoneal mesh repair, have been found in the literature. Assessment as to whether laparoscopic herniorrhaphy could replace conventional repair as the method of choice for inguinal hernia awaits properly organized prospective studies.

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Case report

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Liver resection for recurrent hilar cholangiocarcinoma

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Hilar cholangiocarcinoma is a rare lesion that accounts for less than 2 per cent of all tumours and 10 per cent of liver cancers[1]. It carries a poor prognosis, and surgical resection offers the only chance of cure[2]. Because of the anatomical location of the tumour, carcinoma cells spread via the lymphatics to the caudate lobe. This pattern of spread may increase the possibility of tumour recurrence after local resection if the hilum is resected without concomitant hepatectomy[3]. However, long-term survival has been achieved in a small percentage of patients managed by hilar resection alone[3,4]. The treatment of local recurrence usually consists of percutaneous external biliary drainage or surgical bypass procedures.

A case is reported of hilar cholangiocarcinoma treated with local resection. The tumour recurred and was subsequently treated successfully with a repeat resection including extended right hepatectomy.

Case report

A 56-year-old man underwent operation in June 1991 for hilar cholangiocarcinoma causing obstructive jaundice. The tumour was located at the biliary convergence and local resection was performed. Biliary continuity was established by bilateral hepatojejunostomy using a Roux-en-Y jejunal loop. Histopathological examination confirmed the presence of well differentiated cholangiocarcinoma, with infiltration of the proximal resection margin. The patient made a smooth recovery and was discharged without further therapy. At 10 months the man developed several episodes of acute cholangitis. Percutaneous transhepatic cholangiography showed a short tight stricture affecting the right anterior and posterior sector ducts, suggesting tumour recurrence (*Figure 1*). Retrograde filling of the left duct from the jejunal loop showed this anastomosis to be normal. An external–internal drain was inserted to relieve the cholangitis. Visceral angiography revealed no arterial or portal vascular encasement. Computed tomography (CT) excluded secondaries in the hepatic parenchyma. No attempt was made at this stage to obtain a tissue diagnosis.

Because of the good general condition of the patient and his motivation, a decision was taken to operate and resect the hilar recurrence in May 1992. At laparotomy there was no evidence of peritoneal seeding or lymphadenopathy. Tumour recurrence was confirmed by frozen-section examination. The liver was mobilized and the hilar tumour resected in continuity with an extended right hepatectomy. The tumour was adherent to but not invading the portal vein. During the dissection the jejunal loop was mobilized, but the left hepatojejunostomy was left undisturbed. The patient had an uncomplicated postoperative recovery and was discharged home on day 10. The pathology report on the resected tumour showed features of well differentiated cholangiocarcinoma without involvement of the resection margin, so no adjuvant therapy was given. Some 10 months later the man remains well with normal carcinoembryonic antigen levels and no sign of tumour recurrence on CT.

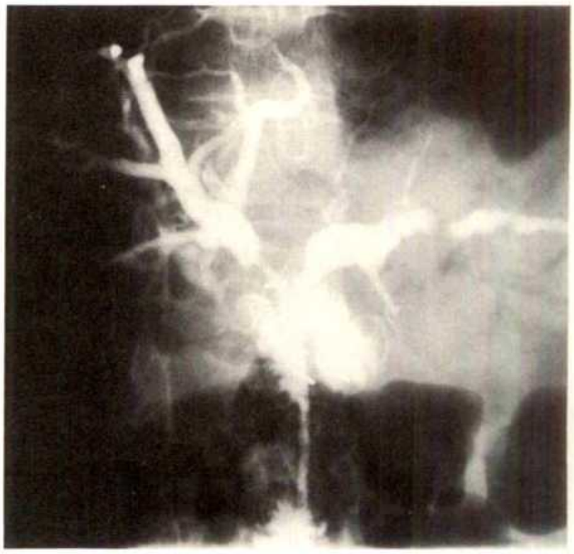

Figure 1 *Percutaneous transhepatic cholangiogram showing a short stricture affecting the right anterior and posterior sector ducts consistent with recurrent cholangiocarcinoma*

Discussion

Surgical resection is the only curative treatment for hilar cholangiocarcinoma. The role of repeat operation and liver resection for treatment of recurrent hilar cholangiocarcinoma is not well documented[2,3]. Most patients develop local recurrence at the anastomosis after resection for hilar cholangiocarcinoma. Usually, previous surgery and the spread of the tumour preclude re-resection, and patients are treated by percutaneous external drainage. Analysis of several large series published in recent years does not provide information on the feasibility of this therapeutic option[1–5]. In the patient presented, recurrence was confined to the right hepatojejunal anastomosis and major liver resection was undertaken with satisfactory results.

Radical extended resection of cholangiocarcinoma is a more complex surgical procedure than localized hilar resection and hence is associated with a high mortality rate, although it gives the best survival figures[2]. The main rationale for operative treatment in the era of interventional radiology is to aim for prolonged survival. This goal is better achieved by radical than local palliative resection[3].

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Changing trends in the management of extrahepatic cholangiocarcinoma

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A series of 107 patients with cholangiocarcinoma diagnosed between January 1980 and December 1991 is reported. Changing patterns of investigation and treatment in the periods 1980–1985 and 1986–1991 are analysed. There was a decrease in the use of percutaneous transhepatic cholangiography in the second period (86 versus *51 per cent of patients) but increased use of endoscopic retrograde cholangiography (19* versus *71 per cent) and computed tomography (8* versus *59 per cent). The overall resectability rate (17 per cent) was similar to those of other reported series but greater in the second period (8* versus *21 per cent). Palliation by endoscopic and percutaneous stenting was associated with a high incidence of recurrent cholangitis (55 per cent) and jaundice (35 per cent). During the second 6-year period, more effective palliation was achieved by segment III cholangiojejunostomy with a lower incidence of recurrent cholangitis (19 per cent) and jaundice (19 per cent). Overall prognosis for patients with this condition is grim and efforts must usually be aimed at providing the most appropriate palliation.*

Carcinoma involving the extrahepatic bile ducts carries a poor prognosis, with fewer than 30 per cent of patients surviving for more than 5 years even in selected groups[1,2]. The tumour is frequently diffuse and sclerotic in nature, tending to invade locally and involve the hilum of the liver. As a consequence, resectability rates under 20 per cent are common[3–6] and efforts are more often aimed at the relief of obstructive jaundice. In recent years, wider application of new imaging techniques has led to improved diagnosis of the cause of the bile duct obstruction. However, investigations such as percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiography (ERC) are invasive and the complications that may follow their use can compromise further management. A 12-year experience in the management of patients with cholangiocarcinoma of the extrahepatic bile ducts has been reviewed in an attempt to improve future management of the condition.

Patients and methods

The case records of 107 patients with extrahepatic bile duct carcinoma diagnosed between January 1980 and December 1991 were identified from unit discharge summaries and operation notes. All patients had been admitted under the care of two consultant surgeons in the University Department of Surgery at Glasgow Royal Infirmary (January 1980 to September 1988) or the University Department of Surgery at the Royal Infirmary, Edinburgh (October 1988 to December 1991). No change in approach to the diagnosis and treatment of these tumours was apparent following the authors' move to Edinburgh.

The extent and type of investigations undertaken in patients referred from other hospitals and before transfer varied. Before 1985, ultrasonography was used to confirm the presence of an obstructed biliary tree and PTC to define the level and nature of the obstruction. Patients with tumours not amenable to resection underwent palliation by surgical insertion of a U tube or by jejunal anastomosis to the common hepatic duct. From 1985, ERC was used to demonstrate the site of obstruction of the biliary tree and PTC reserved for patients in whom endoscopic evaluation was unsuccessful or unsatisfactory. Patients considered unfit for surgery underwent stenting by endoscopic or percutaneous means, or by a combination of both techniques. Computed tomography (CT) and angiography were used to assess suitability for resection. Patients who were fit for surgery but with an irresectable tumour underwent segment III cholangiojejunostomy. Tumours were considered irresectable when metastases were present in the liver or extrahepatic disease was seen on CT. Extensive bile duct involvement on one side of the liver with vascular involvement on the other, evidence of encasement of the common hepatic artery and involvement of the main portal vein on angiography were also taken as signs of irresectability. Liver resection was deemed necessary where there was involvement of the biliary tree beyond the second bifurcation. To demonstrate the changing trends in management, the 37 patients treated before January 1986 were compared with the 70 managed from January 1986 to December 1991.

Clinical presentation, radiological investigation and pathology results were reviewed retrospectively from case records. In addition, the site of tumour, form of treatment and resulting complications were noted. Tumours were classified using the method described by Longmire[7]: 'upper' third tumours involved the common hepatic duct above the level of the cystic duct, 'middle' third lesions affected the supraduodenal portion of the common bile duct and 'lower' third tumours involved the retroduodenal and intrapancreatic portions of the common duct. 'Diffuse' tumours were those involving more than one-third of the extrahepatic bile ducts. Long-term morbidity and mortality were documented from outpatient and inpatient attendance, and by questionnaires completed by the patient's general practitioner when hospital follow-up was not possible.

Operative mortality was defined as that within 30 days of surgery. The following postoperative complications were documented: cholangitis (rising serum bilirubin level above normal laboratory range in association with pyrexia, rigors and upper abdominal pain), acute pancreatitis (serum amylase level above 1000 units/l), an intra-abdominal collection (abdominal pain, pyrexia and collection seen on ultrasonography), biliary peritonitis (clinical signs of peritonism associated with tachycardia, pyrexia and confirmed at autopsy in one case), septicaemia (general deterioration in clinical state associated with pyrexia, tachycardia, hypotension and growth of one organism on repeat blood culture), chest infection (pyrexia, purulent sputum, clinical and radiological evidence of acute pulmonary consolidation), wound infection (erythema with production of pus from the wound), superficial wound dehiscence (breakdown of skin apposition in the healing wound), cardiac failure (dyspnoea, orthopnoea, pitting peripheral oedema with radiological confirmation), myocardial infarction (chest pain, serial electrocardiographic changes, acute rise in serum cardiac enzyme levels), cardiac arrest (clinical and electrocardiographic evidence of disruption of normal cardiac rhythm), pulmonary embolus (chest pain, dyspnoea, central cyanosis, tachycardia and collapse with confirmation at autopsy), cerebrovascular accident (deterioration in conscious state, development of neurological signs lasting more than 24 h), bleeding peptic ulcer (lesion seen at endoscopy following haematemesis), urinary

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tract infection (dysuria, frequency and growth of bacteria on culture) and acute renal failure (urine output less than 400 ml per day associated with rising urea and creatinine levels).

The χ^2 test was used to examine changing trends in diagnosis and treatment and to compare the incidence of cholangitis between groups. The log rank test was used for comparison of survival curves, which were prepared from Kaplan–Meier life-tables.

Results

A total of 107 patients (63 men, 44 women) with a diagnosis of cholangiocarcinoma were identified. The mean age at diagnosis was 65 (range 35–90) years. Sixteen patients were admitted directly to the surgical unit, eight transferred from medical wards within the hospital and 83 transferred from other hospitals.

Fourteen patients had undergone a procedure involving the biliary tract before admission: four had received cholecystojejunostomy, two choledochojejunostomy, four operative placement of a stent and three non-operative stent insertion. Another patient had undergone cholecystectomy, open biopsy of cholangiocarcinoma situated in the common hepatic duct and placement of a T tube.

The time from first admission to the authors' unit until definitive treatment ranged from 0 to 47 (mean 9) days. The length of stay in the unit ranged from 4 to 101 (mean 23) days.

A diagnosis of cholangiocarcinoma was confirmed histologically or cytologically in 67 per cent of cases. In 53 of the 57 patients from whom material was obtained for histological evaluation, the diagnosis of cholangiocarcinoma was confirmed. Malignant cells were seen in fine-needle aspirates in 15 of the 23 patients from whom material was obtained for cytological evaluation. Six patients had the diagnosis confirmed at post-mortem examination. Patients who did not have positive pathological confirmation of cholangiocarcinoma had typical radiological features on cholangiography and the subsequent clinical course was consistent with a primary bile duct tumour.

Table 1 *Investigations used in the management of patients with cholangiocarcinoma*

	1980–1985 ($n=37$)	1986–1991 ($n=70$)	Total ($n=107$)
Percutaneous transhepatic cholangiography	32 (86)	36 (51)	68 (64)
Endoscopic retrograde cholangiography	7 (19)	50 (71)	57 (53)
Computed tomography	3 (8)	41 (59)	44 (41)
Angiography	2 (5)	21 (30)	23 (21)

Values in parentheses are percentages

Table 2 *Treatments used in the management of patients with cholangiocarcinoma*

	1980–1985 ($n=37$)	1986–1991 ($n=70$)	Total ($n=107$)
No treatment or laparotomy only	11	4	15 (14)
Extrahepatic bypass	14	5	19 (18)
Operative stent insertion	8	1	9 (8)
Segment III cholangiojejunostomy	1	18	19 (18)
Resection	3	15	18 (17)
Endoscopic and/or percutaneous stent insertion	0	27	27 (25)

Values in parentheses are percentages

Jaundice was a presenting feature in all but one patient. The highest bilirubin level for each patient in the week before surgery (or in the first week after admission if no operation was performed) varied between 7 and 785 (mean(s.d.) 346(218)) μmol/l.

The investigations performed before and after referral are shown in *Table 1*. Although 64 per cent of patients underwent PTC, this procedure was used less frequently in the period 1986–1991. The use of ERC increased after 1985 and CT was employed much more frequently in the second period under review. The change in use of all three of these investigations was significant ($P<0{\cdot}001$). Angiography was also used more frequently after 1985 ($P<0{\cdot}01$).

Sixty-nine tumours (64 per cent) involved the upper third of the extrahepatic biliary tree, eight (7 per cent) the middle third, ten (9 per cent) the lower third and 20 lesions (19 per cent) were diffuse. Of the 20 patients with diffuse cholangiocarcinoma, only two had tumours that did not involve the upper third of the biliary tree and seven had tumours that involved the upper, middle and lower thirds. There was a clear predominance of tumours involving the upper biliary tract (81 per cent), reflecting the high proportion of tertiary referrals (85 per cent).

The number of patients who received no treatment or underwent laparotomy only decreased in the period 1986–1991 (*Table 2*). There was a reduction in the number of extrahepatic bypass procedures performed and the number of operative stents inserted after 1985, while only one segment III cholangiojejunostomy was performed before 1986. The trend was significant for all three of these treatment groups ($P<0{\cdot}01$).

In the period 1980–1985, three bile duct resections were undertaken and consisted of excision of tumour involving the confluence of the right and left hepatic ducts. In the years 1986–1991, six such local resections were performed, six hemihepatectomies undertaken (because of local hepatic invasion of hilar tumour) and three pancreatoduodenectomies performed for tumours of the lower biliary tree with local pancreatic invasion. This increase in the resectability rate from 8 to 21 per cent was not, however, significant ($P>0{\cdot}05$).

Biliary stenting was not employed before 1986 but thereafter its use increased significantly ($P<0{\cdot}001$). Twenty-seven patients had non-operative stent insertion: 14 at ERC, nine by a combination of ERC and PTC, and four by PTC alone.

The incidence of postoperative or postintervention complications is shown in *Tables 3* and *4*. Six patients experienced cholangitis within 7 days of treatment: operative extrahepatic bypass (one), segment III bypass (one), resection (one) and ERC–PTC stenting (three). Another patient developed acute pancreatitis following ERC stenting and required pancreatic necrosectomy at the time of resection of a hilar bile duct tumour with left hemihepatectomy. Two patients developed anastomotic leakage and an intra-abdominal collection following

Table 3 *Treatment, outcome and positive pathological diagnosis rate in 107 patients with cholangiocarcinoma*

	No. of patients	30-day mortality*	Complications*	Positive pathology*	Median (range) survival (months)
No treatment or laparotomy only	15	11 (73)	4 of 7 (57)	8 (53)	0·5 (0–9)
Extrahepatic bypass	19	3 (16)	6 (32)	11 (58)	5 (0·5–49)
Operative stent insertion	9	1 (11)	4 (44)	7 (78)	9 (1–16)
Segment III cholangiojejunostomy	19	3 (16)	7 (37)	17 (89)	5 (0–18)
Resection	18	3 (17)	9 (50)	18 (100)	14·5 (0–114)
Endoscopic and/or percutaneous stent insertion	27	7 (26)	11 (41)	10 (37)	3·5 (0–14)

*Values in parentheses are percentages

Table 4 *Treatment, outcome and positive pathological diagnosis rate in 69 patients with upper third cholangiocarcinoma*

	No. of patients	30-day mortality*	Complications*	Positive pathology*	Median (range) survival (months)
No treatment or laparotomy only	10	7 (70)	2 of 3 (67)	6 (60)	0·5 (0–5)
Extrahepatic bypass	8	1 (12)	2 (25)	6 (75)	5 (0·5–6)
Operative stent insertion	8	1 (12)	4 (50)	6 (75)	11 (1–16)
Segment III cholangiojejunostomy	13	1 (8)	1 (8)	12 (92)	5 (0·5–18)
Resection	10	1 (10)	4 (40)	10 (100)	16 (1–32)
Endoscopic and/or percutaneous stent insertion	20	5 (25)	9 (45)	9 (45)	4 (0–11)

*Values in parentheses are percentages

Table 5 *Incidence of cholangitis, jaundice and abdominal pain after treatment for cholangiocarcinoma in patients surviving beyond 30 days*

	No. of patients	Cholangitis	Jaundice	Pain
Extrahepatic bypass	16	3 (19)	6 (38)	3(19)
Operative stent insertion	8	6 (75)	1 (12)	1(12)
Segment III cholangiojejunostomy	16	3 (19)	3 (19)	2(12)
Resection	15	1 (7)	1 (7)	4(27)
Endoscopic and/or percutaneous stent insertion	20	11 (55)	7 (35)	9(45)

Values in parentheses are percentages

Table 6 *Incidence of cholangitis, jaundice and abdominal pain after treatment for upper third cholangiocarcinoma in patients surviving beyond 30 days*

	No. of patients	Cholangitis	Jaundice	Pain
Extrahepatic bypass	7	1 (14)	3 (43)	2(29)
Operative stent insertion	7	5 (71)	0 (0)	1(14)
Segment III cholangiojejunostomy	12	3 (25)	2 (17)	1 (8)
Resection	9	1 (11)	0 (0)	3(33)
Endoscopic and/or percutaneous stent insertion	15	8 (53)	6 (40)	7(47)

Values in parentheses are percentages

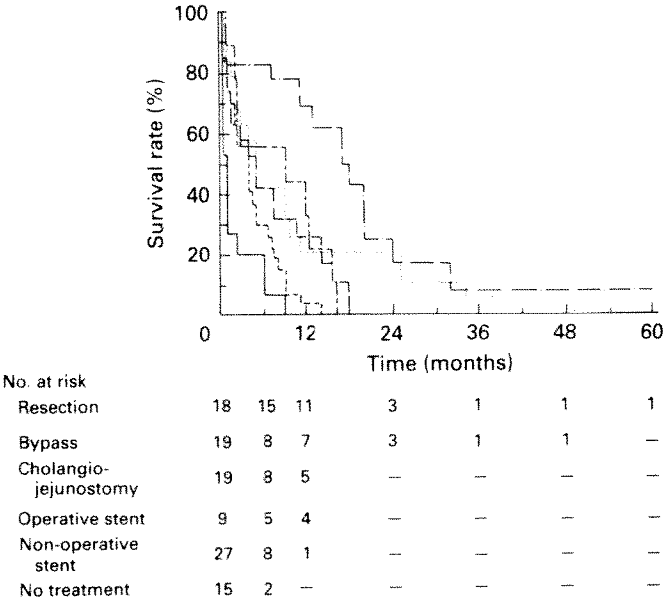


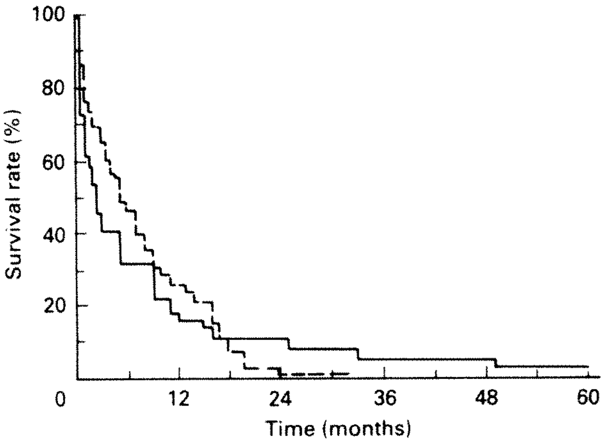
Figure 1 *Kaplan–Meier survival curves for six treatment groups of patients with cholangiocarcinoma. ——, No treatment; – – –, segment III cholangiojejunostomy; -----, endoscopic and/or percutaneous stent insertion; — – —, operative stent insertion; —·—, resection; ·····, extrahepatic bypass. Eight patients are still alive: extrahepatic bypass, one at 16 months; segment III cholangiojejunostomy, one at 14 months; and resection, six at 7, 8, 14, 15, 18 and 19 months*

resection of a hilar tumour, while two cases of biliary peritonitis and one of septicaemia followed non-operative stenting. Another patient suffered a fatal cerebrovascular attack 6 days after an extrahepatic bypass procedure. Two patients were found to have an endoscopically confirmed bleeding peptic ulcer in the immediate postoperative period; one gastric ulcer followed hemihepatectomy and the bleeding responded to injection sclerotherapy, and the other followed a segment III bypass and the bleeding point was under-run at operation. One patient died from a pulmonary embolus following surgical placement of a stent. Three patients were treated for cardiac failure (laparotomy only, extrahepatic bypass, segment III bypass) and another was resuscitated from a cardiac arrest during attempted extrahepatic bypass and so underwent laparotomy only. Antibiotics were used for one urinary tract infection (extrahepatic bypass) and two patients required medical management of acute renal failure (operative stent insertion, segment III bypass). The remaining complications were chest infection (14), wound infection (seven) or dehiscence (two), and fatal myocardial infarction following resection (one).

Ten patients died within 30 days of attempted resection or surgical palliation (*Tables 3* and *4*), with an operative mortality rate of 15 per cent. In addition, four of the seven patients undergoing laparotomy only and seven of the 27 undergoing non-operative stent insertion died within 30 days. The 30-day mortality rate for all patients with cholangiocarcinoma was 26 per cent. The operative mortality rate for each of the four surgical treatments was similar. The number of patients developing complications in each of these groups was also similar (*Table 3*).

The operative mortality rate for patients undergoing resection was 17 per cent overall, and 10 per cent for those with tumours involving the upper third of the biliary tract. Sixteen of the 18 resections were performed with macroscopically clear resection margins at laparotomy. Ten of these 16 patients also had clear resection margins on histological examination. The presence of clear margins has not significantly prolonged survival but six patients are alive to date. Two of the 18 patients who underwent resection died from postoperative sepsis. One patient died from local recurrence of tumour, four died with liver metastases and five died with widespread metastatic disease associated with local recurrence in two.

Recurrent symptoms in patients who survived more than 30 days are shown in *Tables 5* and *6*. Patients who underwent surgical bypass or resection of tumour and who survived to leave hospital had a significantly lower incidence of recurrent cholangitis (seven of 47) than those undergoing non-operative (11 of 20; $P<0·001$) or operative (six of eight; $P<0·001$) stent insertion. All patients who developed recurrent cholangitis following surgical bypass of the tumour had undergone PTC or ERC before operation. After successful segment III bypass one patient developed multiple abscesses in the right hemiliver



No. at risk							
1980–1985	37	12	7	4	2	2	1
1986–1991	70	34	18	2	–	–	–

Figure 2 *Kaplan–Meier survival curves for patients with cholangiocarcinoma in the periods 1980–1985 (——) and 1986–1991 (– – –). Eight patients treated in 1986–1991 are still alive at 7, 8, 14, 14, 15, 16, 18 and 19 months*

while another developed a cholecystoduodenal fistula. Six of the 11 patients who developed cholangitis following non-operative stenting had the prosthesis changed but two died as a consequence of the complication. Three patients required more than one change of stent. In total, 36 prostheses were used for 27 patients, although the number of stents used in each patient did not affect long-term survival.

Long-term survival following the different forms of treatment for all patients is shown in *Tables 3* and *4*. Patients who underwent resection had the longest duration of survival ($P < 0{\cdot}03$). There was no difference in long-term survival between patients having other forms of surgical palliation and, although survival in all these groups was longer than that in patients undergoing non-operative stenting, the difference was not significant. *Figure 1* shows the survival curves for each of the six treatment groups. Two patients were still alive after extrahepatic and segment III bypass at 16 and 14 months respectively. Six patients were still alive after resection at 7, 8, 14, 15, 18 and 19 months. *Figure 2* compares the survival curves for the two periods under review. The median survival period for 1980–1985 was 2·5 (range 0–114) months and for 1986–1991 5 (range 0–32) months, but eight patients are still alive in the second interval under review. There was no significant difference in duration of survival between the two time periods.

Discussion

Primary carcinoma of the biliary tract is an uncommon cause of obstructive jaundice but carries a poor prognosis. The majority of patients die within 6–12 months of diagnosis[8,9] and, although some series have reported survival rates of up to 30 per cent at 5 years in those undergoing attempted curative resection[1,2], the overall 5-year survival rate has previously been reported[3,10] as less than 10 per cent.

Jaundice is absent in 2–10 per cent of cases at the time of diagnosis of bile duct cancer[3,11,12] since incomplete obstruction may occur involving only the right or left hepatic duct[13]. Many patients admit to long-standing abdominal pain or dyspepsia; the one anicteric patient in the present series presented with upper abdominal pain and deranged liver function test results.

Ultrasonography is accepted as the initial imaging procedure in jaundiced patients. It may demonstrate bile duct dilatation and give an indication of tumour extent or even resectability[4,14,15]. It has been suggested that Doppler ultrasonography may, in experienced hands, yield clinically useful information about vascular invasion and obviate the need for angiography in the assessment of resectability[16].

More detailed information on the level of obstruction can be obtained by percutaneous or endoscopic cholangiography. It has been stated that PTC allows preoperative determination of the proximal extension of the tumour into the liver, but the procedure is not without significant risk and may introduce infection into an obstructed biliary tree. ERC is also associated with considerable morbidity[17–19] as a large volume of contrast medium has to be injected through the obstruction if the distended proximal biliary tree is to be visualized, and the proximal extent of the tumour cannot always be determined. This procedure does permit the option of stenting, but we believe that its use should be restricted to palliation in unfit patients with irresectable low bile duct tumours.

Good-quality CT may obviate the need for PTC or ERC by demonstrating the level of obstruction and involvement of the caudate lobe[15]. It may determine the presence of metastatic invasion of the liver and exclude left hepatic lobe atrophy, which would prevent useful decompression via the segment III duct. Arteriography and portography have also proved useful in assessing resectability. Vascular involvement of one side of the liver with extensive bile duct involvement on the other side, or involvement of both main branches or the main trunk of the portal vein, are taken as signs of irresectability[20]. Several authors[21–24] have suggested diagnostic strategies in jaundice, and the formulation of an ordered use of radiological investigations would be of clear benefit in selecting appropriate treatment.

There is considerable debate as to whether preoperative biliary drainage diminishes postoperative morbidity and reduces the operative mortality rate in patients submitted to surgery for obstructive jaundice. However, prospective controlled studies have not shown a reduced surgical morbidity rate in patients undergoing preoperative external drainage[25,26] and there is a significant incidence of complications related to the drainage procedure itself[27]. Czerniak and Blumgart[4] concluded that preoperative external drainage in obstructive jaundice is not indicated except in patients with cholangitis who have developed sepsis. Furthermore, the present authors' experience has demonstrated that attempted drainage of the right system may compromise the option of using a segment III duct should the tumour prove irresectable.

The resectability rate for hilar cholangiocarcinoma remains low at 15–20 per cent, even in specialized centres with an interest in the condition[3–6,28]. The degree of ductal involvement and evidence of vascular invasion will influence the extent of resection required. Involvement of the biliary tree beyond secondary bifurcations usually indicates the need for hepatic resection[5,29]. Caudate lobe involvement may be discovered only at laparotomy and will influence the decision to proceed to resection[5,30], but some would now advocate routine removal of this lobe when resection is contemplated[31]. In recent years, intraoperative ultrasonography has been of value in assessing the extent of local invasion and in determining whether radical resection with excision of the caudate lobe or segment III cholangiojejunostomy should be undertaken[32].

Resection of hilar tumours carries considerable morbidity[33], which is often related to leakage of bile at the anastomosis. Reports of hospital mortality rates vary from 0 to 27 per cent in large series[3,8,28,34]. Of the 18 patients who underwent resection in the present series, three died within 30 days of operation, although only one operative death occurred since 1985. Eleven of the patients undergoing resection died within 3 years, although one-third of patients are still alive. Czerniak and Blumgart[4] reviewed a number of series which reported that resection of hilar cholangiocarcinoma was associated with a survival rate of 30 per cent at 3 years and of 12 per cent at 5 years. More recent series have reported a 5-year survival rate of up to 30 per cent for patients undergoing resection[1,2] and a median survival period of between 6 and 24 months[28,35–37]. The present median survival time of 18 months for the nine patients with upper third cholangiocarcinoma treated by resection and surviving to leave hospital is similar. If long-term survival is to be improved, resection must be associated with tumour-free margins on histological examination. The present series does not show significantly prolonged survival in such patients but others have reported an improved survival rate when histologically tumour-free resection margins have been achieved[28]. Although some support a more radical surgical approach to the treatment of cholangiocarcinoma, this has not been associated with an obvious increase in curative resection or survival rates[35]. None the less, excision of tumour offers the only prospect of cure, and in the present series resection provided the most effective form of palliation. The unchanged long-term survival in the two consecutive 6-year periods (*Figure 2*) underlines the need for successful and long-lasting palliation in most of these patients.

When resection is not feasible, biliary decompression may be achieved by one of several methods of surgical bypass[6,8]; evidence[20,29,38] suggests that drainage of only part of the liver suffices to relieve jaundice and pruritus, provided the undrained remnant is not infected and the drained liver not atrophic. Approaching the left hepatic duct through the umbilical fissure (segment III cholangiojejunostomy) has become popular by achieving satisfactory results with a low operative morbidity rate[39,40]. The 30-day mortality rate associated with this procedure in the present series was 16 per cent; this value is in keeping with those in other reports[4,5,8,41], where the 30-day mortality rate ranged between 0 and 31 per cent. Alternative surgical procedures such as the Longmire approach have not been widely taken up. In the authors' experience, bypass procedures with anastomosis to the extrahepatic biliary tract do not provide adequate palliation as there is a high risk of recurrent cholangitis and jaundice owing to the proximity of the anastomosis to the tumour. Terblanche and colleagues[42] have popularized the use of surgically placed catheters for drainage, and various modifications have subsequently been described[8], but we have been disappointed by the quality of palliation with these U tubes. Advances in radiological and endoscopic intubation have reduced the need for these procedures in patients who are not suitable for segment III bypass or who are unfit for surgery.

There is considerable debate as to whether bypass surgery is superior to non-operative stenting[43]. A number of authors[5,44,45] strongly support surgical palliation because of the apparent improvement in duration and quality of survival, despite conclusions by others[46,47] in favour of endoprostheses. There are no controlled data to support either view in the management of hilar cholangiocarcinoma but, in the present series, patients were more likely to suffer cholangitis following non-operative stenting. One advantage of managing patients by an operative approach is the ease with which tissue may be obtained for histological examination. The lack of tissue diagnosis in one-third of the present patients is disconcerting but similar to findings of previous reports[48]. Thirty-five of the present patients did not undergo laparotomy and obtaining pathological confirmation of diagnosis in these is notoriously difficult[49]. In other series, confirmation of diagnosis has been better when patients have been managed surgically[20]. In addition, a number of other conditions such as lymphoma and metastatic breast carcinoma may mimic cholangiocarcinoma, and their treatment and subsequent prognosis are quite different.

Endoprostheses may be inserted endoscopically or percutaneously. Quality of life with endoprostheses appears to be superior to that with external drains, although their exchange is less easy. External drains may lead to metabolic derangement, may become infected and require daily care. Hilar tumours may be more difficult to traverse with the endoscopic technique, and the authors have found a combined percutaneous and endoscopic approach[50] useful. In 13 of 27 patients undergoing non-operative stenting of a high hilar lesion, it was not possible to insert the prosthesis by endoscopic means alone. There is a significant risk of septicaemia or pancreatitis associated with ERC[18,19]. Percutaneously or endoscopically inserted stents may become blocked or infected, necessitating repeated hospital admission for the patient. The complication and 30-day mortality rates observed in the present series (41 and 26 per cent respectively) are marginally higher than those of 10–30 per cent and 20–30 per cent reported by others[8,46,51,52].

Patients with irresectable tumours have a poor long-term prognosis and, until recently, treatment has been aimed at palliation of symptoms. However, radical resection combined with liver transplantation has been proposed as an option for patients without distant metastases. Although initial outcome has been disappointing[53–55], careful patient selection may lead to more favourable results[56].

The search for better palliation of bile duct cancer has prompted the use of radiotherapy in several centres. External radiation alone proved unsatisfactory and techniques involving the use of iridium-192 wire, inserted either percutaneously or endoscopically, have been developed[57–59]. In addition, the combination of palliative surgery, intraoperative and postoperative radiotherapy has been proposed for advanced tumours[60]. Small numbers of patients, in addition to lack of cytological or histological proof of diagnosis in long-term survivors, make it difficult to draw firm conclusions. Further assessment of long-term benefit is required but such treatment offers some hope in the management of this difficult condition.

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Percutaneous transhepatic cholecystostomy for acute acalculous cholecystitis

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The effectiveness and long-term results of percutaneous cholecystostomy for acute acalculous cholecystitis are evaluated. Fifteen patients with acute acalculous cholecystitis were treated prospectively by this procedure, using a pigtail catheter successfully placed under ultrasonographic and fluoroscopic guidance. Prompt relief of the signs and symptoms of cholecystitis was achieved in 14 patients. One required emergency cholecystectomy for uncontrolled bleeding after drainage. Another patient underwent prophylactic cholecystectomy before further chemotherapy for leukaemia. The remaining 13 patients required no further surgery. Morbidity and mortality rates were 13 per cent and nil respectively. Long-term follow-up showed no recurrence of cholecystitis after removal of the catheter. Percutaneous cholecystostomy is a safe, effective and usually definitive procedure for the treatment of acute acalculous cholecystitis.

Acute acalculous cholecystitis is a serious condition occurring in critically ill patients. The first case was reported[1] in 1844 and the incidence is increasing[2,3]. Risk factors include severe trauma or burns, major surgery, long-term fasting with or without total parenteral nutrition, sepsis, diabetes mellitus, atherosclerotic vascular disease, systemic vasculitis and acquired immune deficiency syndrome[4–14].

Many surgeons recommend early cholecystectomy or early surgical cholecystostomy[2,3,5–7,9,15,16], while some advocate percutaneous cholecystostomy for critically ill patients with acute cholecystitis[14,17–26]. However, the number of patients with acute acalculous cholecystitis treated by percutaneous drainage is too small (eight or fewer in each series[14,18,19,21,22,24]) to clarify the merits and demerits of the procedure. Moreover, long-term follow-up after removal of the percutaneous catheter has not been reported.

Experience of percutaneous transhepatic cholecystostomy in a large series of 15 patients with acute acalculous cholecystitis is reported. The aims were to evaluate the early safety and efficacy and long-term results of percutaneous drainage.

Patients and methods

Between 1982 and 1991 a total of 511 patients with benign biliary disease were treated in this department. During this period, 15 patients (2·9 per cent) with acute acalculous cholecystitis were treated, all of whom are included in this study.

Diagnosis of acute acalculous cholecystitis was made by physical examination and abdominal ultrasonography. Biliary scintigraphy was not performed. Findings suggesting acute cholecystitis on physical examination included right hypochondrial pain, tenderness and/or muscular rigidity located in the right upper quadrant and a palpable distended gallbladder with localized tenderness. Ultrasonographic findings suggesting acute cholecystitis included gallbladder distension, sludge formation, a thickened gallbladder wall (thickness 3 mm or greater), sonographic localization of gallbladder tenderness and a sonolucent layer in the gallbladder wall. Acute acalculous cholecystitis was diagnosed if one or more physical findings and two or more sonographic signs were present in the absence of gallstones. The diagnosis of acalculous cholecystitis was confirmed when no gallstones were identified in imaging studies including postdrainage cholangiography and in the resected gallbladder (two cases). Non-specific physical findings associated with acalculous cholecystitis included nausea, vomiting, abdominal distension, fever (temperature 37°C or greater), and leucocytosis (white cell count over 10^{10}/l).

A prospective protocol of management was followed, using percutaneous transhepatic cholecystostomy as the first choice of treatment. Biliary drainage was conducted under both ultrasonographic and fluoroscopic guidance. A 7- or 8-Fr pigtail cholecystostomy catheter (Niigata University type; Hanako Medical, Tokyo, Japan) was placed by a two-step method with guidewire exchange. The catheters are 280 mm in length and contain an end hole and four side holes on the inner border of the curved tip to avoid obstruction during drainage. A right intercostal transhepatic approach was used for all drainage procedures; this reduces the risk of catheter dislodgement and decreases intraperitoneal leakage of bile. Aspirated bile was sent for anaerobic and aerobic culture. The position of the catheter was adjusted as necessary during cholecystography at the time of drainage. Definitive cholangiography was performed several days later, after the resolution of acute cholecystitis, to detect any abnormality, including gallstones in the biliary tract.

Results

Patients

The 15 patients comprised 11 men and four women of mean age 56·1 (range 34–75) years. Acute acalculous cholecystitis followed major abdominal surgery in six patients and cardiovascular procedures in four; it developed during intensive medical treatment in five patients (for leukaemia in two, irresectable endometrial cancer in one, sepsis in one, systemic lupus erythematosus in one).

Diagnosis

The clinical manifestations and ultrasonographic findings of acute acalculous cholecystitis are shown in *Table 1*. Signs and symptoms were often difficult to assess in comatose or severely ill patients. Although gallbladder distension and sludge formation were present in all cases, other ultrasonographic findings were not consistent.

Immediate effects of percutaneous cholecystostomy

After catheterization, prompt relief of the signs and symptoms of acalculous cholecystitis was achieved in all but one patient. The single non-responder underwent percutaneous cholecystostomy for cholecystitis occurring during steroid therapy for severe systemic lupus erythematosus. Her condition was complicated by systemic sepsis and pneumonia at the time of drainage. Catheter insertion was followed by immediate arterial bleeding from the gallbladder wall. Blood was aspirated from the catheter. The bleeding could not be managed conservatively and emergency cholecystectomy was performed. Gross examination of the gallbladder revealed gangrenous cholecystitis and bleeding from an eroded branch of the cystic artery.

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Table 1 *Incidence of clinical and ultrasonographic findings in 15 patients*

	Incidence
Clinical examination	
Right hypochondrial pain	14
Localized tenderness	13
Localized muscular rigidity	7
Palpable enlarged gallbladder	5
Nausea and/or vomiting	5
Fever (temperature ≥37°C)	14
Leucocytosis (white cell count $\geq 10^{10}$/l)	13
Ultrasonography	
Gallbladder distension	15
Sludge formation	15
Thickness of wall ≥3 mm	11
Sonolucent layer	10
Pericholecystic fluid	2
Sonographic localization of gallbladder tenderness	5

Acute gangrenous cholecystitis was confirmed by pathological examination.

Complications developed during percutaneous cholecystostomy in two of the 15 patients. One major complication was described above. A second patient had transient haemobilia that settled spontaneously within several hours. Dislodgement of the catheter or bile peritonitis after insertion did not occur. There were no deaths attributable to percutaneous cholecystostomy. The overall morbidity and mortality rates of the procedure were thus 13 per cent and nil respectively.

Two cholecystectomies were performed after percutaneous drainage: one emergency procedure and one elective operation in a patient who suffered acute acalculous cholecystitis in the course of anticancer chemotherapy for leukaemia. This patient underwent uncomplicated percutaneous cholecystostomy that relieved the signs and symptoms. The gallbladder was removed prophylactically as it represented a possible focus of infection following an additional course of anticancer chemotherapy. In the remaining 13 patients, percutaneous cholecystostomy was the definitive treatment and none has required further surgical intervention.

The bile aspirated initially was thick and black in 11 patients and purulent in three. The characteristics of the bile were not recorded in the remaining patient. Cholecystography at the time of drainage was performed in 14 patients; cystic duct obstruction was demonstrated in all cases. Repeat cholecystography was performed several days later in 14 patients and revealed patent cystic and common bile ducts with no calculi in the biliary tract. The colour and viscosity of draining bile returned to normal within 2 or 3 days. Seven of the 15 patients had positive bile cultures. *Enterococcus* was the most common bacterium, detected in six specimens, although two or more bacterial isolates were identified in five of these. *Escherichia coli* was identified in only one specimen.

Long-term outcome

Eight patients in this series died within 1 year of percutaneous cholecystostomy from causes unrelated to acute acalculous cholecystitis. Four of the ten patients with postoperative cholecystitis died within 1 year: three from recurrent cancer at 4, 9 and 11 months, and one from ongoing sepsis and multiple organ failure at 2 months. Four of the five patients in whom acalculous cholecystitis occurred during intensive medical care died from the underlying disease within 1 year. The remaining seven patients have survived 5–75 months after removal of the percutaneous catheter (six patients) or after elective cholecystectomy (one).

Follow-up results of the 13 patients treated with percutaneous cholecystostomy alone are shown in *Figure 1*. To analyse the effectiveness of percutaneous drainage alone, the two patients who subsequently underwent cholecystectomy were eliminated. Long-term follow-up of more than 5 years was possible in five patients (four surgical, one medical). None of the 13 patients has had recurrent gallbladder disease during the follow-up period.

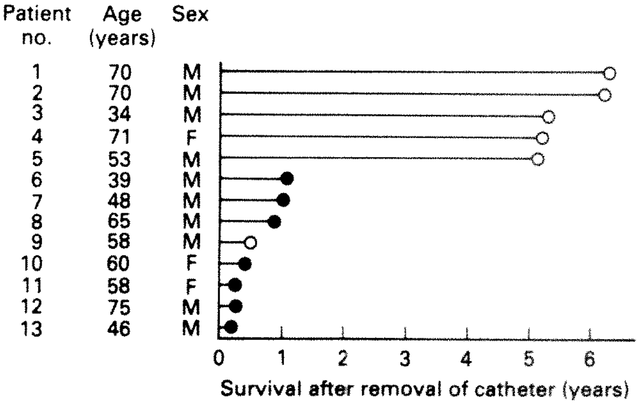

Figure 1 *Outcome in 13 patients treated with percutaneous cholecystostomy alone. ○, Survival without recurrent gallbladder disease at the last follow-up; ●, death from underlying disease. No patient showed recurrence of gallbladder disease during the follow-up period*

Discussion

Many surgeons have advocated early cholecystectomy for acute acalculous cholecystitis because of the rapid progression of the disease[2,3,6,7,9,15,16]. Some have recommended early surgical cholecystostomy for high-risk patients[2,5,9,16]. Percutaneous cholecystostomy has recently been accepted as an alternative to surgery[14,17–26], but the procedure has been limited to critically ill patients. The present authors have adopted percutaneous transhepatic cholecystostomy as the treatment of choice for all patients with acute acalculous cholecystitis.

The patients in this series were predominantly male, consistent with the findings of other authors[5,6,9,14,15,21]. Although Savoca *et al.*[9] showed a preponderance of elderly men with atherosclerotic vascular disease in acalculous cholecystitis, increased incidence was not found in any age group in the present study. Savoca *et al.* found several cases of acalculous cholecystitis in outpatients. In contrast, all those in the present series were inpatients recovering from surgery or under intensive medical care.

Hepatobiliary scintigraphy is thought to be useful in the early detection of cystic duct obstruction[9,27,28]. Ultrasonography can demonstrate pathology of the gallbladder wall, depict the luminal contents and detect pericholecystic lesions[5,7,14,29,30]. Ultrasonography is preferable to cholescintigraphy because it is easily available, it allows detection of concomitant lesions (such as gallstones, abscess or tumour), it is cost–effective, requires a shorter examination time and allows simultaneous therapeutic intervention such as percutaneous drainage[14,18,20,25,26].

Successful catheterization and prompt relief of signs and symptoms were achieved in almost all cases in the present series. These results are similar to those of other reports[14,17–26]. Dislodgement of the catheter is a serious complication of percutaneous cholecystostomy[17,23]. Pearse *et al.*[17] and Klimberg and colleagues[21] recommended use of an accordion catheter to prevent dislodgement. McGahan[23] used a catheter with a Cope-type loop. The present authors use a specially designed pigtail catheter with angulation to prevent dislodgement and have not experienced this complication. Teplick *et al.*[25] reported low morbidity (7·8 per cent) and mortality (0·4 per cent) rates for percutaneous cholecystostomy in a review of 231 patients. The rates of morbidity (including minor complications) and mortality in the present series are similar. Percutaneous cholecystostomy has a lower morbidity and mortality rate[14,19,22,24–26] than surgical cholecystostomy and cholecystectomy[5,9,15], and is therefore advocated as the treatment of choice for acalculous cholecystitis.

The present study confirms previous reports[24,26] that in acute acalculous cholecystitis the aspirated bile is thick and black, and that initial cholecystography demonstrates an obstructed cystic duct, although later repeat cholecystography reveals a patent cystic duct. It may be postulated that the concentrated viscous gallbladder bile with sludge causes pseudo-obstruction of the cystic duct, leading to cholecystitis.

Bile cultures were positive in seven of 15 cases in this series, consistent with several studies which report positive rates ranging from 38 to 100 per cent[5,6,14,15,19,24]. Bile culture may be negative in the early phase of acute acalculous cholecystitis and the overall rate of negative cultures is high. These findings suggest that bacterial infection is secondary in the pathogenesis of such cholecystitis and that negative bile cultures do not exclude the condition. Although *E. coli* has generally been regarded as the most common causative organism of acute acalculous cholecystitis[6,14,15,19], *Enterococcus* was the bacterium most frequently recovered in the present study. Orlando and co-workers[5] and Berger *et al.*[24] also reported the predominance of *Enterococcus* and *Pseudomonas aeruginosa* in critically ill patients. The recovery of these organisms in bile culture suggests that therapies in intensive care may alter the organisms isolated.

The prognosis following percutaneous cholecystostomy for acute acalculous cholecystitis mainly depends on the patient's underlying condition. Long-term results after percutaneous cholecystostomy alone have not been sufficiently reported. The present long-term follow-up data indicate that all patients have been free from recurrent gallbladder disease, including acalculous cholecystitis, during the follow-up period.

Percutaneous cholecystostomy is a safe and effective treatment for acute acalculous cholecystitis. The procedure is usually definitive, requiring no further surgery. Recurrent gallbladder disease, after the removal of the catheter, did not occur in this study population. Percutaneous cholecystostomy is advocated as the treatment of choice for all patients with this condition.

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Temporary use of a biliary endoprosthesis for unsuspected bile duct stones found at laparoscopic cholecystectomy

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Preoperative identification of patients with common bile duct (CBD) stones is often possible using the following criteria[1]: history of jaundice or pancreatitis; abnormal liver function test results; or CBD diameter >5 mm. Nevertheless, the incidence of unsuspected CBD stones is 4–10 per cent in studies that include operative cholangiography as a routine procedure at laparoscopic cholecystectomy[2,3]. This creates a dilemma in laparoscopic cholecystectomy as to whether the surgeon should leave the duct stones and rely on postoperative endoscopic sphincterotomy (ES) to solve the problem. ES is usually a straightforward procedure but occasionally fails, necessitating additional open surgery. Alternatively, the surgeon could deal with the stones immediately and prevent bile duct obstruction in the early postoperative period. Although procedures for laparoscopic CBD stone removal have been reported[3–5], they are difficult to perform and have not become common practice. Conversion to open cholecystectomy is not an attractive option at this stage.

This paper reports adaptation of a well known endoscopic procedure for use in conjunction with laparoscopic cholecystectomy, namely insertion of an endoprosthesis with multiple side holes from the CBD across the sphincter to the duodenum. This manoeuvre prevents obstruction of the bile duct from retained stones, with its risk of cystic duct leakage and cholangitis, and greatly facilitates ES. It allows a safe 'precut' along the prosthesis with a needle papillotome before insertion of a conventional papillotome. The technique virtually eliminates the risk of endoscopic failure.

Patients and methods

A total of 60 patients with gallbladder stones were treated by laparoscopic cholecystectomy using a standard technique. A 5-mm trocar was inserted below the costal margin at the site of the fundus of the gallbladder. Operative cholangiography was attempted in each case by the use of Olsen's forceps and a catheter. If stones were found, a 0·28-mm guidewire was passed through the catheter down the cystic duct and CBD into the duodenum, where it was placed as far distal as possible (*Figure 1a*). The cholangiography catheter was then withdrawn and a straight 5-Fr endoprosthesis (Cook Denmark, Karlslunde, Denmark), 6 cm long with multiple side holes and reference marks at both ends, was introduced through the Olsen forceps over the guidewire. Using the cholangiography catheter, the prosthesis was pushed over the guidewire under fluoroscopic control until it lay with its proximal end in the CBD and its distal end in the duodenum (*Figure 1b*).

At a convenient time after operation, ES was performed. A needle papillotome was first used to cut along the endoprosthesis before insertion of an ordinary papillotome to complete the sphincterotomy. Finally, the CBD stones and endoprosthesis were removed.

Results

Unsuspected bile duct stones were found in three patients (5 per cent); insertion of the endoprosthesis was achieved without problems in all three cases. The maximum time for cholangiography and endoprosthesis insertion was 20 min. Antibiotic cover was given.

The postoperative course was uneventful in each patient. ES was carried out on the first day after operation in two patients, while one had the procedure postponed until day 14 and had no symptoms in the meantime. Each patient was discharged home on the following day, after an uneventful recovery.

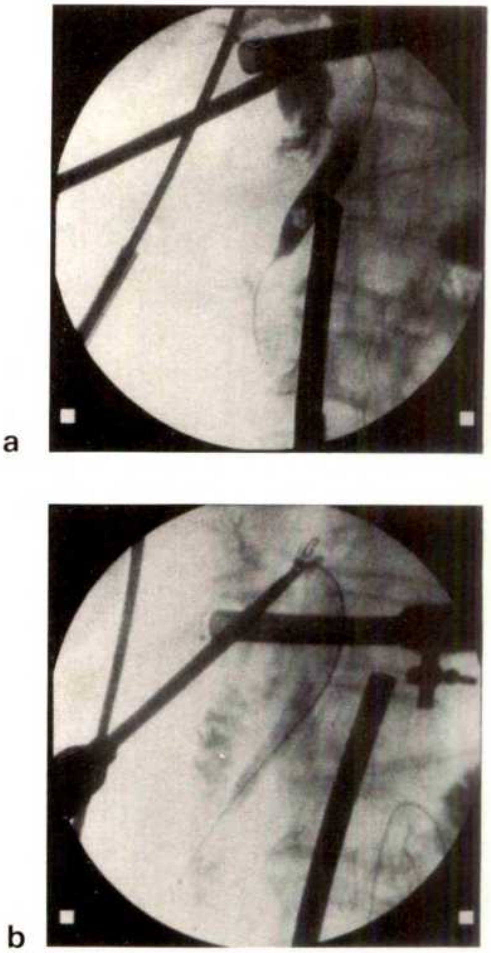

Figure 1 *Plain abdominal radiographs taken during laparoscopic cholecystectomy in a patient with a stone in the common bile duct.* **a** *A guidewire has been passed through the Olsen cholangiography forceps down the common bile duct and into the duodenum.* **b** *A 6-cm 5-Fr endoprosthesis has been passed over the guidewire and placed across the sphincter of Oddi. Note that the guidewire has been passed into the jejunum*

Discussion

During laparoscopic cholecystectomy the introduction of a guidewire with Olsen cholangiography forceps down the bile duct into the duodenum is very simple. Displacement of the guidewire while the endoprosthesis is pushed downwards into the duodenum is effectively prevented by the narrow bile duct, so the time needed is minimal. ES is an accepted treatment for patients with CBD stones and reluctance to use it has vanished with increasing experience. The procedure is safe in skilled hands, and the use of an endoprosthesis as a guide to the CBD enhances this safety.

After more than two decades of the widespread use of ES in the treatment of patients with CBD stones, no serious long-term effects have emerged from the lack of a sphincter

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between the bile duct and duodenum. Nevertheless, most endoscopists restrict the procedure to patients above the age of 40 years. It is among this group of patients that CBD stones are most frequent. Complicating factors such as extreme obesity may justify sphincterotomy for stones at an even younger age.

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Surgical workshop

Br. J. Surg. 1993, Vol. 80, November, 1444

Laparoscopic ligation of large pedicles

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In laparoscopic surgery it is difficult to apply ligatures. Various techniques and devices such as the Roeder knot and the Endoloop (Ethicon, Edinburgh, UK) have been developed. These have limitations in that the Roeder knot is time consuming in application and the Endoloop requires that the structure to be secured has a free end over which the loop can be passed. An alternative method of inserting a strong ligature is described that does not suffer from these disadvantages and which may have important applications.

Surgical technique

Tie-wrap fasteners are widely used in engineering to secure wires together. A tie wrap can be passed down a 10-mm laparoscopy cannula to be applied internally. An applicator 'gun' has been developed that inserts the tie wrap and then secures it.

The tie wrap is mounted in the applicator gun by its locking square and passed tail-first through the laparoscopy cannula to the pedicle or structure to be secured. The tail is picked up with a grasping forceps and passed around the pedicle, then fed into the locking square (*Figure 1*). The tie is tightened by pulling the tail up the applicator gun shaft using a trigger-operated ratchet mechanism. When the ligature has reached the required tension, a guillotine blade cuts off the excess tail which is then removed with the applicator gun (*Figure 2*).

Discussion

The authors have used tie wraps to occlude the oesophagus during thoracoscopic oesophagectomy and found them to be easily applied, strong and secure. A tie manufactured from biodegradable material could be left in the body without fear of late complications. Tie wraps may be suitable for a wide variety of applications, such as ligating vascular pedicles or occluding the cystic duct, appendix, oesophagus or bowel. They can be used in open surgery but their action makes them ideally suitable for the limited access available during laparoscopic procedures.

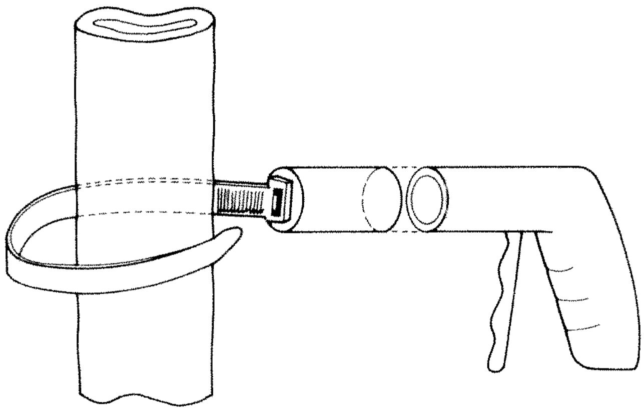

Figure 1 *Application of the ligature*

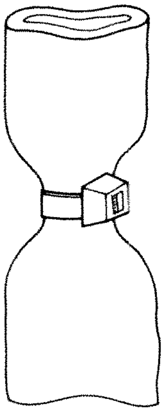

Figure 2 *Secured ligature*

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Mucosal morphology, cell proliferation and faecal bacteriology in acute pouchitis

A study was performed to investigate whether acute reservoir ileitis (pouchitis) is associated with specific changes in mucosal morphology, crypt cell kinetics and faecal bacteriology in the ileal pouch. Forty-six patients were studied (ileal reservoir, 36; end ileostomy, ten) using clinical grading, sigmoidoscopy and biopsy; 24 patients with a reservoir were restudied after therapy for 1 month with metronidazole 400 mg three times daily. An index of villus atrophy and crypt cell production rate (CCPR) were determined in all biopsy material. Faecal bacteriology was assessed in 12 patients with a pouch before and after metronidazole therapy. The mucosa of patients with pouchitis was associated with a lower villus atrophy index ($P = 0{\cdot}052$), a higher CCPR ($P = 0{\cdot}03$) and a higher grade of acute inflammation than that in those without pouchitis. There was no difference in faecal bacterial counts between patients with and without pouchitis. A low atrophy index correlated with a high CCPR ($P < 0{\cdot}001$), worse functional score ($P < 0{\cdot}001$) and more severe pouch mucosal acute inflammation ($P < 0{\cdot}001$), but not with faecal bacteriology. Following metronidazole therapy there was resolution of acute pouch inflammation, increased villus atrophy index ($P = 0{\cdot}049$), decreased CCPR ($P = 0{\cdot}049$) but no differences in faecal bacterial counts apart from Bacteroides *species. These data show that metronidazole therapy does not specifically alter the growth of common faecal bacteria in patients with pouchitis, apart from* Bacteroides *species. However, metronidazole causes resolution of the typical changes in pouch mucosal morphology and crypt cell kinetics associated with pouchitis.*

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Restorative proctocolectomy is now a realistic option in the elective surgical management of selected patients with ulcerative colitis and familial adenomatous polyposis[1]. However, changes occur in the ileal mucosa after reservoir construction (villus atrophy and crypt hyperplasia) that render its morphology similar to that of colonic mucosa[2]. Chronic inflammation is found in almost all ileal reservoir biopsies, while the association of an acute inflammatory infiltrate in patients with pouch dysfunction is characteristic of pouchitis[3].

Although the mechanisms of the mucosal morphological changes in ileal reservoirs are unknown, increased numbers of anaerobic bacteria have been found in reservoir effluent compared with those seen in an ileostomy[4]. Villus atrophy is severe in pouchitis[5] but faecal stasis and bacterial overgrowth may not be aetiological factors[6,7]. It is possible that the morphological changes of pouch ileum in pouchitis represent mucosal adaptation to a new luminal bacterial environment[7]. Alternatively, the infrequent reports of pouchitis in patients without a previous history of ulcerative colitis suggest the possibility of reactivation of such colitis in colonic metaplasia, but this hypothesis does not explain the clinical and endoscopic resolution of pouchitis after metronidazole therapy.

This study was designed to investigate whether acute reservoir ileitis is associated with specific changes in mucosal morphology, crypt cell kinetics and faecal bacteriology in the ileal pouch before and after metronidazole therapy.

Patients and methods

Forty-six patients were selected for the study, of whom 36 had an ileal pouch and ten an end ileostomy. Clinical features were matched as closely as possible and no patient had an ileal resection >5 cm. The 36 patients with an ileal pouch underwent a personal interview at which a pro forma was completed. A clinical score was subsequently compiled for each patient, with each of ten items scoring one point: daytime soiling (controlled with one pad), nocturnal soiling, change of pads (for a single soiling episode), daily antidiarrhoeal medication, lack of discrimination between flatus and faeces, profuse soiling (uncontrolled by multiple pad changes), severe urgency (<10 min), daytime frequency of defaecation >7, night-time frequency of defaecation >2, and 24-h frequency of defaecation >9.

Pouch endoscopy was performed by one author (W.A.K.) in all patients using a paediatric sigmoidoscope, and an acute inflammatory grade was recorded: loss of vascular pattern, 1; mucosal granularity, 2; contact haemorrhage, 3; spontaneous haemorrhage, 4; mucosal ulceration, 5; surface mucopus, 6.

Two large biopsies were taken from each pouch and terminal ileum using Officer biopsy forceps. The ileum in the patients with an ileostomy was healthy and uninflamed. Biopsies were taken from specific areas of the pouch and the ileostomy 10 cm from the anal verge or stoma. One biopsy was placed in formalin for histological analysis; the other was halved and used separately to measure crypt cell production rate[8] (CCPR) and villus atrophy index.

The 36 patients with a pouch were subdivided into those with (12) and those without (24) pouchitis. A sigmoidoscopy score ≥3 and an acute histology score (see below) ≥3 was used to define pouchitis. The 24 patients without pouchitis were further grouped into those with a good (12) or a poor (12) functional result from restorative proctocolectomy using a clinical score ≥3 to define a poor result. The four study groups were well matched for age, sex, diagnosis, pouch design and length of follow-up (*Table 1*). Random stool culture in all patients before the start of the study did not reveal any enteropathogenic organism.

Twenty-four patients (12 with pouchitis, 12 with a poor result) underwent a repeat study after therapy for 1 month with metronidazole 400 mg three times daily. Repeat sigmoidoscopy after treatment was performed by an independent observer (R.T.) who was not aware of the initial findings. Concurrent assessment was performed by W.A.K.

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Table 1 *Clinical details of the patient study groups*

		No pouchitis		
	Pouchitis ($n = 12$)	Poor function ($n = 12$)	Good function ($n = 12$)	Ileostomy ($n = 10$)
Age (years)*	27 (24–40)	32 (24–44)	31 (22–44)	33 (30–55)
Sex ratio (M:F)	8:4	8:4	8:4	6:4
Diagnosis				
Ulcerative colitis	11	11	11	9
Familial adenomatous polyposis	1	1	1	0
Constipation	0	0	0	1
Pouch design				
W	4	4	4	
J	8	8	8	
Follow-up (months)*	6 (6–18)	6 (6–18)	6 (6–18)	6 (6–18)

*Values are median (range)

and R.T. in 12 of these 24 patients. There was a good correlation between the two observers for sigmoidoscopy score ($\rho = 0{\cdot}97$, $P < 0{\cdot}001$).

All patients provided informed consent and the study was approved by the Central Birmingham Health Authority Ethical Committee.

Bacterial counts

Counts[9,10] of all aerobic and anaerobic bacteria isolated from the pouch were made in 12 of the 24 patients (six with and six without pouchitis) before and after metronidazole therapy. Six other patients with a pouch in the good-function group had pouch samples collected on 3 consecutive days at a specific time in the day, while taking their normal diet, to measure day-to-day variability in bacterial count.

All faecal samples were processed within 5 min of collection. A 1-g sample of faeces was mixed with 9 ml glycerol broth, and 1 ml of this suspension was snap-frozen at −70°C in duplicate for 1 week. The two samples were thawed, pooled and a 0·02-ml drop of dilute faeces used to isolate *Salmonella* and *Shigella* on Selenite and Rappaport media. Serial tenfold dilutions of the faecal suspension were made, from 10^{-1} to 10^{-8}, and two drops inoculated on to a range of aerobic and anaerobic media. Aerobic plates were initially incubated at 37°C for 24 h and, if there was no growth at this stage, reincubated for a further 24 h. Anaerobic plates were incubated in an anaerobic cabinet for 48 h at 37°C and, if negative, reincubated for a further 96 h. All isolated organisms were identified by the morphological appearance of the colonies, by the appearance after Gram staining and by standard biochemical testing[10]. Quantitative results are shown as logarithmic colony-forming units of organisms per gram of ileal stool.

Histology

Each biopsy was oriented under a dissecting microscope and embedded in paraffin so that the mucosa was uppermost. Perpendicular sections from the middle of the block were cut, stained with haematoxylin and eosin, and mounted. Only sections with at least ten villi and an intact muscularis mucosa were retained.

Sections were assessed in random order by a pathologist (H.T.) without access to clinical information. Sections taken before and after therapy with metronidazole were scored as follows: polymorph infiltration – none, 0; mild, 1; moderate plus crypt abscess, 2; severe plus crypt abscess, 3; and surface ulceration – none, 0; <25 per cent, 1; 25–50 per cent, 2; >50 per cent, 3.

Villus atrophy index

Black and white photographs of each section at a magnification range of ×48–75 were taken and used to quantify the degree of villus atrophy by computerized morphometry using the Reichert–Jung Kontron IBAS 1 image analyser (Germany). The computer software was calibrated to account for photograph magnification and initial pixel units converted into millimetres.

Measurements were made of the total mucosal surface length (MS), area of lamina propria (LP) and total crypt area (CA) over at least ten villi. The ratio of MS/(LP − CA) was used as an index of villus atrophy[4,11].

Crypt cell production rate

Fresh biopsy material was incubated in organ culture medium[8]. After 15 h, the medium was replaced with identical fresh medium to which vincristine 0·4 μg/ml had been added. The explants were removed at hourly intervals 1–3 h after reincubation, placed in Carnoy's fixative (six parts ethanol, one part acetic acid, three parts chloroform) for 2–6 h and stored in 70 per cent ethanol.

Crypt microdissection was performed by an independent person (D.Y.) unaware of the clinical outcome. After rehydration and hydrolysis, the biopsy was stained in Schiff's reagent. The number of arrested metaphase figures in ten crypts for each time point were counted and recorded as the mean metaphase number per crypt. Counts from crypts with either anaphase or telophase figures were discarded. The mean number of metaphase figures per crypt was plotted against time and the slope of the line, determined by linear regression, provided the CCPR[12].

Representative tissue explants were prepared for transmission electron microscopy before and after organ culture. The sections were examined by a specialist in electron microscopy.

Statistical analysis

Unless otherwise indicated, grouped data were expressed as the median and approximate 95 per cent confidence interval. Differences between two independent groups were assessed using the two-sample Wilcoxon test and those between more than two independent groups using rank one-way analysis of variance (Kruskal–Wallis test). Differences between paired groups were analysed using the paired Wilcoxon test. Significance was set at a two-tailed value of $P < 0{\cdot}05$.

Linear regression lines were plotted using the method of least squares. The significance of association was measured using the Spearman rank correlation coefficient.

Results

Assessment of tissue viability by transmission electron microscopy showed that after incubation for 15 h the nuclear and cytoplasmic ultrastructure of the brush border glycocalyx and microvillus were well preserved. Crypt cell morphology before incubation in organ culture was normal, with tissue and organelle integrity remaining unaltered after incubation.

Faecal bacteriology

There was no significant day-to-day variation in either total anaerobe ($P = 0{\cdot}355$) or aerobe ($P = 0{\cdot}058$) numbers (*Table 2*), or in individual species counts of *Escherichia coli*, enterococci (*Streptococcus faecalis*) and *Bacteroides*. These three species were the only organisms isolated in all three faecal samples from the six patients studied. Other aerobic isolates found in some but not all samples were: *Proteus* species, non-haemolytic streptococci, *Klebsiella* species and lactobacilli; other anaerobic isolates were *Bifidobacterium*, *Proprionibacterium*, *Clostridium* and *Peptostreptococcus* species[13]. To minimize intraperson variability only total aerobic and anaerobic bacterial counts and individual species counts of *E. coli*, *S. faecalis* and *Bacteroides* were studied further.

There was no significant difference in the total aerobic ($P = 0{\cdot}11$) or anaerobic ($P = 0{\cdot}75$) bacterial counts between the six patients with and the six without pouchitis (*Table 3*). There was also no difference in the numbers of *E. coli* ($P = 0{\cdot}46$), *S. faecalis* ($P = 0{\cdot}20$) or *Bacteroides* species ($P = 0{\cdot}75$) between these two patient groups.

Table 2 *Faecal bacterial validation data over 3 consecutive days*

	Day 1	Day 2	Day 3
Total aerobes ($n = 6$)	4·81–9·40	4·99–8·40	6·18–8·40
Total anaerobes ($n = 6$)	6·98–9·36	4·40–8·54	7·44–9·70
Escherichia coli ($n = 6$)	4·70–7·63	4·43–6·70	4·70–7·40
Streptococcus faecalis ($n = 6$)	4·11–9·40	4·40–8·40	4·81–8·40
Bacteroides ($n = 6$)	6·98–9·11	4·40–8·48	7·40–9·70

Values are ranges in $\log_{10}$ [colony-forming units per g]

Table 3 *Faecal bacterial counts in patients with and without pouchitis*

	Pouchitis	No pouchitis
Total aerobes	8·22 (6·35–10·02)	7·55 (6·20–8·44)
Total anaerobes	8·16 (4·17–10·02)	8·20 (7·02–10·22)
Escherichia coli	7·18 (4·40–8·17)	6·50 (4·70–7·70)
Streptococcus faecalis	8·20 (6·30–8·47)	6·52 (6·17–8·36)
Bacteroides	7·90 (4·17–9·09)	8·17 (4·11–9·81)

Values are median (95 per cent confidence interval) $\log_{10}$ [colony-forming units per g]

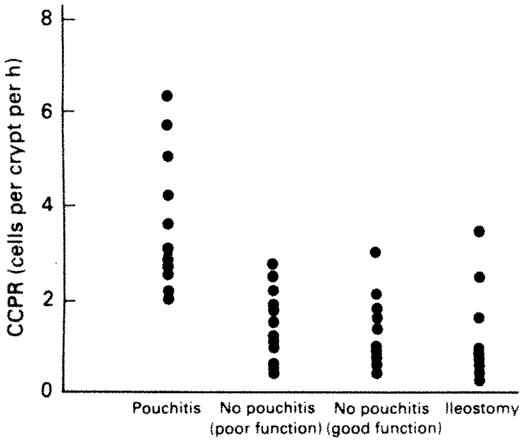

Figure 1 *Crypt cell production rate (CCPR) in patients with and without pouchitis and in those with an ileostomy.* P = *0·03 (Kruskal–Wallis analysis of variance)*

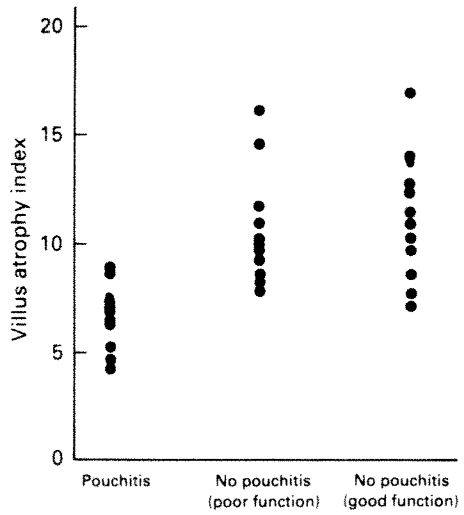

Figure 2 *Villus atrophy index in patients with and without pouchitis.* P = *0·052 (Kruskal–Wallis analysis of variance)*

Pretreatment assessment

There was no significant difference in the median (range) functional score between the 12 patients with and the 12 without pouchitis (5 (5–8) *versus* 4 (3–6) respectively, $P = 0.35$). The median (range) sigmoidoscopy score in patients with pouchitis was significantly higher (4·5 (3–6)) than that in those without (1 (0–2)) ($P = 0.02$). The median (range) histology score in patients with pouchitis (3·5 (3–6)) was significantly higher than in those without (1·5 (0–3)) ($P = 0.046$).

The CCPR was significantly higher in patients with pouchitis than in both those with no pouchitis and those with an ileostomy (median (range) 3·1 (1·8–6·6), 1·4 (0·4–2·8) and 1·1 (0·5–2·9), and 0·8 (0·2–3·4) respectively, $P = 0.03$) (*Figure 1*). The villus atrophy index was lower in patients with pouchitis (signifying a greater degree of atrophy) than in those without (median (range) 6·7 (4·1–8·2) *versus* 9·5 (6·7–17·1) and 11·8 (6·2–17·8), $P = 0.052$). Although this difference was not statistically significant, the distribution of the data suggests a possible type II error (*Figure 2*).

There was a negative correlation between CCPR and villus atrophy index ($\rho = -0.82$, $P < 0.001$). There was also an inverse correlation between the atrophy index and: (1) the functional score ($\rho = -0.59$, $P < 0.001$); (2) the acute histology score ($\rho = -0.64$, $P < 0.001$); and (3) the sigmoidoscopy score ($\rho = -0.69$, $P < 0.0001$). There was no apparent correlation between the villus atrophy index and any bacterial count: total aerobes, $\rho = -0.40$; total anaerobes, $\rho = -0.48$; *E. coli*, $\rho = -0.42$; *S. faecalis*, $\rho = -0.46$; *Bacteroides* species, $\rho = -0.54$.

Longitudinal studies

In the 12 patients with pouchitis, the functional score fell from a median (range) of 5 (5–8) before to 3 (1–4) after metronidazole therapy. The median (range) sigmoidoscopy score fell after metronidazole from 4·5 (3–6) to 2 (1–3) (*Figure 3*) and the histology score also fell from 3·5 (3–6) to 1 (1–3) after metronidazole therapy (*Figure 4*). In contrast, in patients without pouchitis there was no significant change in the median (range) functional score before and after metronidazole therapy (4 (3–6) *versus* 3 (2–4)), sigmoidoscopy score (1 (0–2) *versus* 0·5 (0–2)) or histology score (1·5 (0–3) *versus* 1 (0–3)).

There was a significant decrease in the median (range) CCPR in patients with pouchitis, from 3·1 (1·8–6·6) to 1·1 (0·4–3·0) after therapy for 1 month with metronidazole ($P = 0.049$). In contrast, in the 12 patients without pouchitis there was no significant change in the median (range) CCPR before and after metronidazole therapy (1·4 (0·4–2·8) *versus* 1·2 (0·4–1·8), $P = 0.54$) (*Figure 5*). The villus atrophy index also increased significantly, from 6·7 (4·1–8·2) to 12·1 (6·7–14·3) ($P = 0.049$), in patients with pouchitis following metronidazole

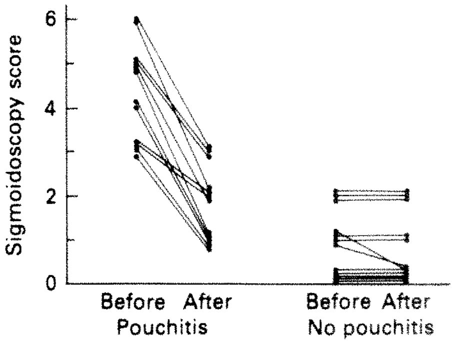

Figure 3 *Sigmoidoscopy score before and after metronidazole therapy in patients with and without pouchitis*

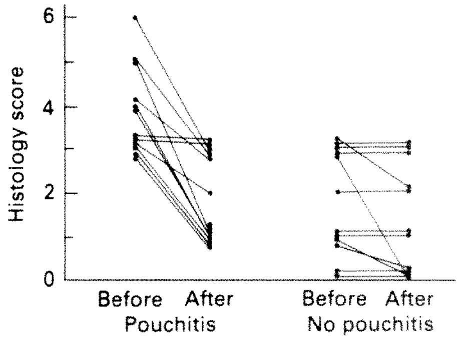

Figure 4 *Histology score before and after metronidazole therapy in patients with and without pouchitis*

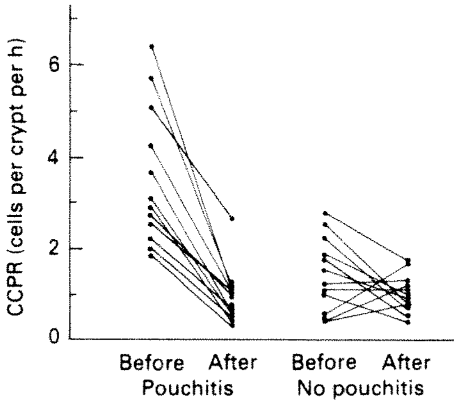

Figure 5 *Crypt cell production rate (CCPR) before and after metronidazole therapy in patients with and without pouchitis*

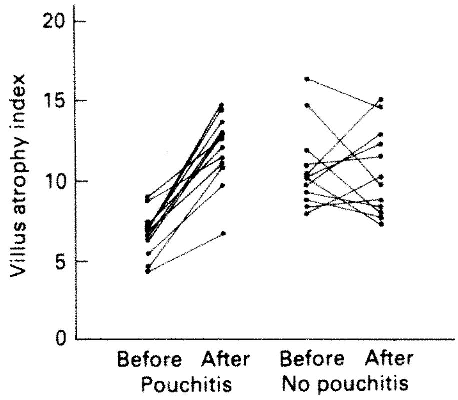

Figure 6 *Villus atrophy index before and after metronidazole therapy in patients with and without pouchitis*

therapy, suggesting that remission of pouchitis is associated with villus regrowth. However, there was no change in atrophy index after metronidazole in patients without pouchitis (9·5 (6·7–17·1) before *versus* 9·4 (6·4–15·8) after therapy, $P = 0{\cdot}17$) (*Figure 6*).

Despite the reduction in CCPR and increase in villus atrophy index following metronidazole therapy in patients with pouchitis, there was no significant difference in total faecal aerobic and anaerobic bacterial counts after metronidazole[13], either in the six patients with or the six without pouchitis. There was also no difference in the counts of *E. coli* and *S. faecalis* in these patient groups following metronidazole administration. As expected, metronidazole had a significant influence on the counts of *Bacteroides* species, which were eliminated by the drug.

Discussion

This study shows that a low villus atrophy index (indicating severe atrophy) and a high CCPR in the ileal pouch mucosa are associated with endoscopic and histological features of pouchitis. These mucosal morphological and cell kinetic changes also occur in active ulcerative colitis[14]. Computer-aided microscopy was used in the present study to minimize observer bias in the measurement of villus atrophy index. This estimate of atrophy has been shown to correlate with other estimates measured morphometrically using linear and eyepiece graticule techniques[11].

Assessment of the rate of cell division[15] provides more dynamic information than does reliance on proliferative state measurement alone. CCPR takes account of the three determinants of cell proliferation, changes in cell cycle time, growth fraction and crypt cell population size[12,14], but is not a sensitive measure of proliferation because large differences are required in linear regression models before significance is obtained[16].

The severe villus atrophy seen in patients with pouchitis confirms the observations of others[7]; also, the negative correlation between atrophy index and CCPR has previously been shown in ileal pouch mucosa. Crypt cell hyperplasia may indicate attempted mucosal regeneration[17,18]. The regrowth of intestinal villi and reduction in CCPR after metronidazole therapy in patients with pouchitis implies that the treatment allows resolution of villus atrophy and normalization of crypt proliferation, as in pouchitis the villi are shed and the crypts hyperactive in an attempt to replace them.

The variable changes in the villus atrophy index and CCPR after metronidazole therapy in patients without pouchitis have three possible explanations. The first is that patient compliance with metronidazole was poor. This explanation is unlikely as *Bacteroides* species were eliminated from the stool in the 12 patients studied following metronidazole treatment. The second interpretation is that quantitative differences exist in bacterial counts to account for the different morphological responses to metronidazole. It has been shown that the total number of bacterial counts and the anaerobe:aerobe ratio in faeces are greater in patients with a continent ileostomy or pelvic ileal pouch[4,19] than in those with an ileostomy[20]. Acute mucosal inflammation has also been shown to be associated with increased faecal bacterial counts in patients with a pelvic ileal pouch and a Kock continent ileostomy by some[21,22] but not by others[4,23].

The present study did not demonstrate any correlation between mucosal morphology and pouch faecal aerobic and anaerobic bacterial counts in patients with and without pouchitis before and after metronidazole therapy. These findings must be interpreted cautiously as faecal bacterial transport and culture provide a very different environment to that of the intestinal lumen. Thus, *in vivo* factors that control bacterial growth may be absent *in vitro*[4]. However, the low numbers in this part of the study raise the possibility of a type II statistical error. These observations do not exclude other qualitative differences in faecal bacteria or their metabolites as important in the aetiology of pouchitis.

The third interpretation of this variable response to therapy postulates that pouchitis is specific to patients with ulcerative colitis. In this setting, metronidazole would act by suppressing cell-mediated immunity rather than by any specific antibacterial mechanism[24]. Although pouchitis is much more common after colectomy for ulcerative colitis, sporadic reports exist of pouchitis following colectomy for familial adenomatous polyposis[25,26]. Furthermore, therapy with metronidazole does not seem to be effective in severe ulcerative colitis[27] and, unlike pouchitis, disease remission in this condition is not associated with either decreased CCPR or mucosal regeneration.

The present study indicates that metronidazole therapy, apart from eliminating *Bacteroides* species, does not specifically alter the growth of other intestinal bacteria in patients with pouchitis. However, metronidazole does result in resolution of the typical changes in pouch mucosal morphology and cell kinetics seen in pouchitis. Although the aetiology of pouchitis remains uncertain, these data suggest that *Bacteroides* species may cause pouchitis in predisposed individuals by an interaction with an as yet unidentified faecal or mucosal factor.

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One-layer continuously sutured colonic anastomosis

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A continuous single-layer suture is rarely used for colonic anastomosis, perhaps both from fear of imperilling perfusion of the cut ends and from anxiety that purse-stringing might occur and cause stricture.

Long experience of the method, however, has reassured the senior author (W.H.F.T.) that neither contingency need be expected. Therefore, when a simple means was appreciated of treating the irksome part of hand-sutured gut union, namely the mesenteric border – particularly when fat laden – and the 'posterior wall' in pelvic anastomosis, it was decided that a prospective assessment should be undertaken. This was started in February 1989 and the 200th anastomosis completed in July 1992. The series was consecutive and unselected, although ten further anastomoses were constructed otherwise by trainees unfamiliar with the technique.

All anastomoses involved the colon but none was extraperitoneal (where other techniques were employed). Preoperative bowel purgation and on-table orthograde colonic lavage were used for left-sided resection. Difficult pelvic anastomoses were protected by wide-bore tube caecostomy.

Table 1 shows the distribution of anastomoses. Operation was performed in 154 patients with carcinoma, 27 with diverticulitis and nine with Crohn's disease. There were ten other miscellaneous colonic lesions. The procedure was classified as urgent in 26 patients: 17 with obstruction (15 carcinoma, two Crohn's disease), four with volvulus, three with

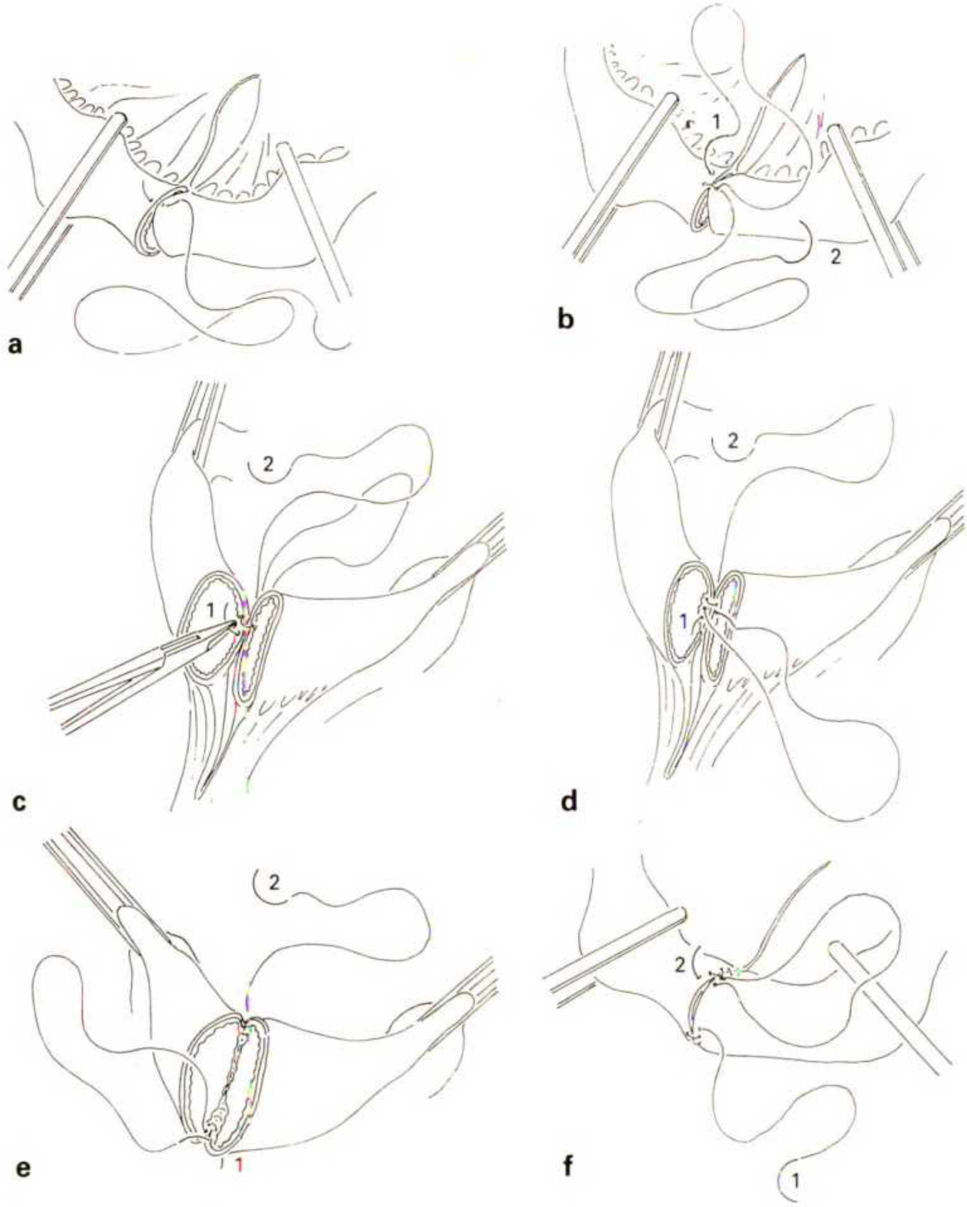

Figure 1 *Technique facilitating one-layer extramucosal continuously sutured intestinal anastomosis. See text for details. Intestinal clamps, shown for orientation, are in fact seldom used*

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Table 1 *Type of anastomosis and outcome*

Site	Procedure	No.	Leak
Ileocolic	Right hemicolectomy	80	2
	Bypass	5	0
Colocolic	Transverse colectomy	3	0
	Left hemicolectomy	18	0
	Sigmoidectomy	55	0
Colorectal	Rectosigmoid	25	0
	Reverse Hartmann's	10	2
	Total colectomy (ileorectal)	4	0
Total		200	4

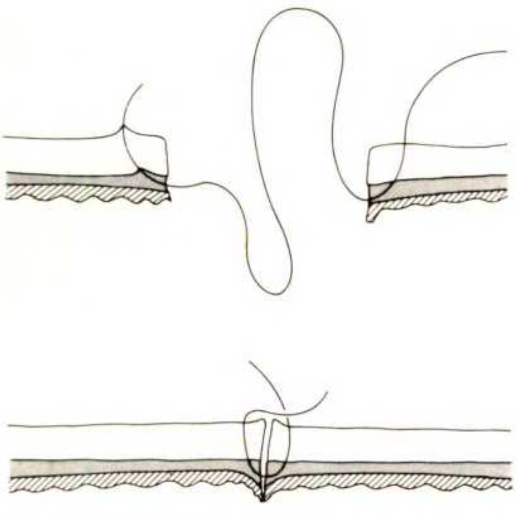

Figure 2 *Extramucosal suture placement*

diverticulitis and one each with caecal carcinoma and caecal diverticulitis. The median age was 68 (range 16–89) years.

Surgical technique

Using a double-ended absorbable monofilament, the stitch starts with a knot on the serosal surface to join the bowel ends midway between mesenteric and antimesenteric borders (*Figure 1a*). Needle 1 passes back through the seromuscular layer to emerge extramucosally at the cut edge of the bowel and on the surgeon's left (*Figure 1b*) to begin the 'back wall' stitch. This can then proceed comfortably, carrying the needle from right to left and towards the surgeon, on the luminal aspect (*Figures 1c–e*) with unimpaired vision along the mesenteric border. When needle 1 has finished on the serosal surface of the right-hand bowel end, needle 2 completes the encirclement, again being passed from right to left and towards the surgeon, although now on the serosal aspect, to finish the anastomosis with a second knot (*Figure 1f*).

The sutures are lightly drawn to appose, but not to crush, the cut ends, and are kept extramucosal so that as the edges are brought together (*Figure 2*) the mucosa is pushed up to create a flutter valve, further enhancing anastomotic security. The submucosa is picked up in the stitch.

Results

Table 1 shows the outcome. Three of the four leaks occurred in extenuating circumstances (resection through an abscess cavity, long-term high-dosage steroid medication, reversal of a low Hartmann's procedure in an infirm, obese, elderly patient). The patient taking steroids died. These three patients were operated on by the consultant surgeon. The fourth, minor, leak followed right hemicolectomy and was the only one generated by a trainee surgeon. No clinical evidence of stricture has occurred.

Discussion

Extramucosal suturing may contribute to anastomotic safety by avoiding transmural puncture and by apposing undamaged vascularized edges, as well as acting as a flutter valve. Matheson *et al.*[1] advocated extramucosal sutures and Halsted[2] showed over 100 years ago the greater importance of the submucosa. Both used interrupted stitches. However, continuous suturing has been found to be as safe as an interrupted procedure in rats[3], and Max and colleagues[4] experienced only a 1 per cent leakage rate in 1000 continuously sutured intestinal anastomoses.

The leak rate in the present study (2 per cent) is acceptable given the greater age of the patients. The method is straightforward to perform and teach, and appropriate to both elective and emergency work. Its speed approaches that of a stapled anastomosis and it is, of course, much cheaper.

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Conservative treatment for low rectal carcinoma by local excision with or without radiotherapy

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Thirty-seven patients with low rectal carcinoma were treated by transanal resection between January 1979 and December 1988. Adjuvant radiotherapy was used in eight patients before operation, in 13 after operation and six patients had both preoperative and postoperative radiotherapy. The selection criteria for transanal resection were low, superficial tumours treated conservatively with curative intent (group 1, 18 patients) or patients medically unfit for (12) or refusing (seven) abdominoperineal resection (APR) (group 2, 19 patients). In group 1, the local recurrence rate was 11 per cent with an overall 5-year survival rate of 100 per cent. In group 2, the local recurrence rate was 53 per cent with an overall 5-year survival rate of 35 per cent. There was no postoperative mortality and minimal morbidity. Salvage of local failure was by APR in six patients. The survival rate after local recurrence was 70 per cent at 1 year and 30 per cent at 5 years. Transanal resection can be proposed as a curative procedure for selected low, small, minimally infiltrating and well differentiated adenocarcinomas. Local control might be improved by postoperative radiotherapy for Astler–Coller stage B_1 tumours or those above 3 cm in diameter. Further trials should examine the results of high-dose (60 Gy) preoperative radiotherapy so that transanal resection might be employed for favourable post-irradiation stage (0 or A) lesions. This new strategy will benefit from a better evaluation of tumour response after primary radiotherapy and an improved assessment of histological excision margins.

Recent advances in understanding of the natural history of low rectal carcinoma and in the surgical technique of coloanal anastomosis have allowed most patients to be treated by anterior resection[1]. However, a minority still require abdominoperineal resection (APR), which entails a permanent stoma and, not infrequently, urinary and sexual dysfunction. Transanal resection has often been explored as a palliative measure. A combination of careful preoperative digital examination with newer imaging techniques (endoluminal ultrasonography, pelvic computed tomography, magnetic resonance imaging) can allow low rectal carcinoma to be staged and its radiosensitivity to be assessed before operation more accurately than previously[2,3]. It is likely that more suitable lesions will be chosen for local treatment in the future[4]. Experience with transanal resection with or without radiotherapy has been reviewed to assess its potential as a curative measure in selected patients.

Patients and methods

Patient population

Thirty-seven patients with a diagnosis of localized, low, resectable adenocarcinoma of the rectum were treated by transanal resection at the Montpellier Cancer Institute between January 1979 and December 1988. Two groups were identified: group 1 consisted of 18 patients (nine men, nine women; median age 59 (range 27–75) years) with small (diameter less than 3 cm), mobile lesions for whom transanal resection was believed to be the treatment of choice. Group 2 comprised 19 patients (11 men, eight women; median age 67 (range 28–77) years) who were either medically unfit for (12) or refused (seven) APR. The median follow-up was 61 (range 24–144) months. Five patients were lost to follow-up or died from unrelated causes. During the study period, 212 patients underwent APR and 225 anterior resection. The transanal approach represented 7·8 per cent of procedures for low rectal cancer. The treatment of choice for small (less than 3 cm in diameter), polypoid, mobile tumours was primary local excision; for larger lesions preoperative radiotherapy was given and following incomplete surgical removal postoperative radiotherapy was recommended.

Tumour location, size and histology

The height from the anal verge to the inferior margin of the tumour was evaluated by clinical examination and rigid sigmoidoscopy. The median distance was 5·7 (range 1–11) cm. Twenty tumours were in the lower, 15 in the middle and two in the upper third of the rectum. The median tumour diameter was 2·5 (range 0·5–6) cm. All tumours were mobile; 24 involved less than half and 13 more than half of the rectal circumference. No tumour was fully circumferential. All lesions were adenocarcinoma: 22 were well differentiated, four moderately differentiated, one undifferentiated and ten had malignant change (more than 50 per cent involvement by cancer) in a villous adenoma.

Therapeutic procedure

Surgery. Local tumour excision was performed transanally, after the anal sphincter had been dilated. Injection of lignocaine (1 per cent) with adrenaline improved haemostasis and visibility. Tumours were removed with an excision margin of no less than 1 cm. When necessary the full thickness of the rectal wall was excised and the resultant defect closed with interrupted 3/0 polyglactin sutures. The excision margins were examined by frozen section for residual disease. A defunctioning colostomy was not used in any patient at the time of primary excision.

Adjuvant therapy. This was used in 27 patients (group 1, 11; group 2, 16): eight before operation (two in group 1, six in group 2), 13 after surgery (seven in group 1, six in group 2) and six both before and after surgery (two in group 1, four in group 2). The radiation was delivered by 15-MV accelerators at 2·2 Gy per day, usually in 18 fractions over 3 weeks, to a total dose of 39·6 Gy. The whole pelvis was treated with a three-field technique. All fields were treated daily and the dose was prescribed to the isodose line, which covered the target volume at risk. Eighteen patients had a further 15-Gy boost directed to the tumour bed. No patient received chemotherapy.

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Follow-up

During the first 2 years, patients underwent clinical examination and estimation of serum markers every 3 months, liver ultrasonography and lung radiography every 6 months, and colonoscopy once a year. After 2 years of follow-up, patients were seen every 6 months for the next 3 years and annually thereafter. Local recurrence was defined as recurrence in the tumour bed or pelvic lymph nodes and was confirmed by guided biopsy. Metastasis represented distant recurrence.

Statistical analysis

Actuarial survival analysis was performed using the Kaplan–Meier method and rates compared using the log rank test. Differences between proportions were analysed by Fisher's exact test; $P<0.05$ was considered significant.

Results

Pathology

Using the Astler–Coller[5] system, the 37 tumours were staged: A, 18; B_1, 14; and B_2, one. Four patients did not have residual tumour after preoperative radiation therapy. Surgical margins were free from tumour in 34 of the 37 specimens. Nodal involvement could not be evaluated because no sampling was done. The tumour stage in each of the patient groups is shown in *Table 1*. There was no difference between the two groups but preoperative radiotherapy was delivered more often in group 2 (53 *versus* 22 per cent).

Table 1 *Treatment and outcome in patients undergoing transanal resection*

	Group 1 ($n=18$)	Group 2 ($n=19$)
Median (range) age (years)	59 (27–75)	67 (28–77)
Preoperative radiotherapy (%)	22	53
Tumour stage		
A	11	7
B_1	5	9
B_2	0	1
No tumour	2	2
Recurrence		
Local	2	10
Metastasis	0	4
Overall survival rate (%)		
3 years	100	50
5 years	100	35

Mortality and postoperative morbidity

There was no perioperative death. Disruption of the rectal suture line occurred in one-third of sutured cases. One patient developed a rectovaginal fistula, which required repair and a temporary colostomy. Three patients complained of radiation proctitis with mild symptoms only.

Sphincter function

No patient developed faecal incontinence necessitating a permanent colostomy. Two patients developed incontinence to flatus, which reduced within 3 months.

Local recurrence (Table 2)

The overall incidence of local failure was 12 of 37: two of 18 in group 1 and ten of 19 in group 2. The two local recurrences in group 1 occurred 47 and 55 months after primary treatment. Salvage of local failure was by APR in a 31-year-old patient and by radiotherapy alone in a 78-year-old. These two patients were free from further disease after follow-up for 85 and 42 months.

In group 2, three of ten local recurrences occurred after incomplete excision. Adjuvant radiotherapy did not prevent progression of the disease and recurrence occurred at 3, 4 and 35 months. Two of these three patients died from local progression. One 68-year-old woman, who initially refused APR for a middle-third carcinoma, was operated on 4 months after transanal excision by anterior resection and low colorectal anastomosis. Among the seven other patients in group 2 who had local recurrence, three had a large stage A tumour (mean diameter 3·9 cm) and three an advanced lesion (stage B_1 after radiotherapy). APR controlled the disease in three patients. The survival rate after local recurrence (*Figure 1*) was 70 per cent at 1 year, 30 per cent at 2 years and 30 per cent at 5 years.

Three patients did not undergo curative treatment of local recurrence and subsequently died from local progression. In nine cases treatment was attempted with a curative goal. APR

Table 2 *Details of 12 patients with locoregional recurrence*

Patient no.	Age at diagnosis (years)	Indication for transanal resection	Tumour stage	Primary therapy	Time to local recurrence (months)	Treatment for local recurrence	Clinical outcome	Length of follow-up (months)
1	77	APR contraindicated	A	Transanal resection	18	55 Gy†	Died with local progression	18
2	76	APR contraindicated	A	Transanal resection	50	Laser	Static disease	17
3	57	APR contraindicated	A	Transanal resection plus 40 Gy	54	APR	Static disease	22
4	61	APR contraindicated	B_1	40 Gy plus transanal resection	8	APR	Died with local progression	14
5	75	Refused APR	B_1	40 Gy plus transanal resection	12	APR	Static disease	60
6	71	Refused APR	No tumour	40 Gy plus transanal resection	32	26 Gy†	Died with local progression	12
7	73	APR contraindicated	B_1	50 Gy plus transanal resection	28	APR	Static disease	51
8	70	Refused APR	A*	Transanal resection plus 55 Gy	35	APR	Died with general progression	13
9	76	APR contraindicated	B*	50 Gy plus transanal resection	3	†	Died with local progression	18
10	68	Refused APR	B_2*	40 Gy plus transanal resection plus 20 Gy	4	Anterior resection	Static disease	22
11	74	Small tumour	A	Transanal resection	47	60 Gy	Static disease	42
12	27	Small tumour	B_1	Transanal resection plus 60 Gy	55	APR	Static disease	85

APR, abdominoperineal resection. *Resection not curative microscopically; †patient refused APR

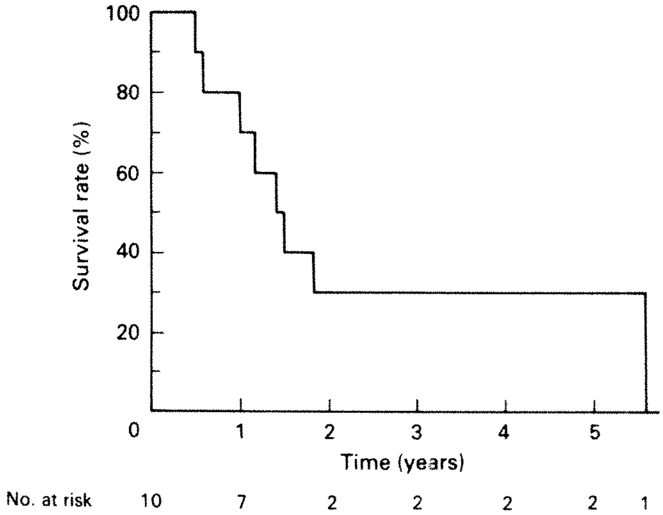

Figure 1 *Survival after locoregional recurrence for patients in group 2*

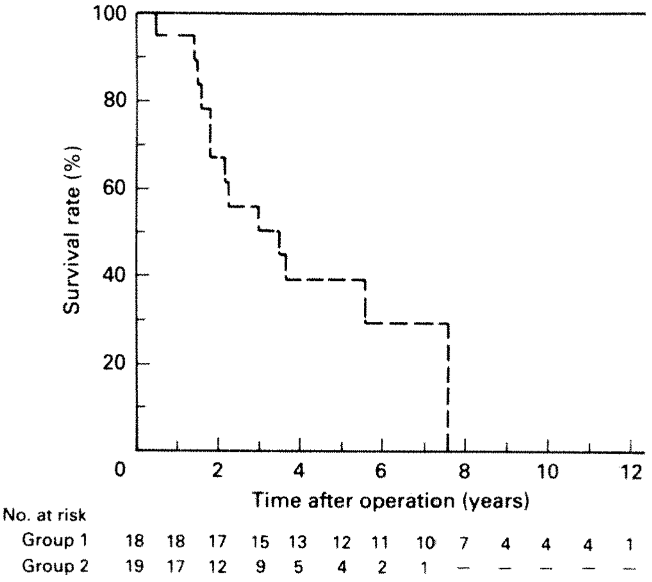

Figure 2 *Overall survival according to the indication for transanal resection:* ——, *group 1 (small tumour);* – – –, *group 2 (abdominoperineal resection contraindicated or refused)*

was performed in six patients; two died, one from local progression at 14 months and one from metastases at 13 months. In patients with stage B_1 and B_2 tumours there was a local recurrence rate of four of nine with 40-Gy adjuvant radiotherapy and five of 18 with 60 Gy. This difference was not statistically significant in such a small number of patients.

Metastases

Metastases occurred only in group 2. The incidence was four of 37; two of these patients had no local recurrence (liver metastases). Only one 28-year-old patient received chemotherapy but did not respond.

Survival

The overall survival rate at 3 years was 74 per cent and at 5 years 68 per cent; the median survival time was greater than 155 months. Survival was significantly ($P<0.001$) better in group 1 than in group 2 (*Figure 2*; *Table 1*). In group 1 the overall 5-year survival rate was 100 per cent, with an 84 per cent disease-free survival rate. In group 2 these values were 35 and 13 per cent respectively. Nine patients died from rectal cancer, giving a rectal cancer-specific mortality rate of 24 per cent: 0 per cent in group 1 and 47 per cent in group 2.

Discussion

Transanal resection for rectal neoplasm aims to restrict the loss of function and to diminish the operative risk. Nevertheless, local tumour excision has to be justified by patient survival rates similar to those achieved by more radical procedures. The reported incidence[6–9] of lesions suitable for transanal resection is variable, ranging from 1·2 to 13 per cent.

Operative deaths after local excision may be avoided, in contrast to reported mortality rates after conventional resection for Dukes' A tumours of 6 per cent[6,8]. In the authors' experience, the length of hospital stay was 23 days for APR, 19·2 days for anterior resection and 9·8 days for transanal excision. Preoperative radiotherapy did not significantly increase this period. In more than 500 patients reported in the literature (*Table 3*), no permanent colostomy for postoperative incontinence was necessary. After transanal resection and postoperative radiotherapy, complications requiring reoperation are infrequent[15,16].

The rate of lymph node metastasis for stage A–B_1 tumours, smaller than 3·0 cm, evaluated after radical resection ranges from 10 to 30 per cent[6,9,10,22,23]. On the other hand, when the tumour invades the perirectal fat, there is nodal involvement in 58 per cent of cases[22,24]. Non-encircling polypoid tumours less than 5 cm in diameter have a lower risk of lymph node involvement, but even tumours confined to the submucosa have lymphatic metastases in 6·5 per cent[6], which is no greater than the operative mortality rate for radical resection in the same series. For small tumours (up to 3·5 cm in size) operated on with radical resection, the incidence of positive lymph nodes rises with increasing tumour penetration[24], high grade[9] or presence of colloid histology[24]. For high-risk patients, excision plus adjuvant pelvic irradiation appears to be a useful form of treatment. Selection criteria for curative local excision must include an assessment of the risk of lymph node involvement.

After local excision, salvage resection has been regarded as a 'back-up' procedure with a reasonable chance of cure. Several authors[11,12,25] have reported that only 50 per cent of local recurrences were operable after curative local excision. Conversely, others have reported satisfactory results after subsequent radical operation[17,26]. In the present authors' experience, APR, whenever possible or accepted by the patient, controlled local progression of the disease in five of six cases. Early diagnosis of local recurrence seems to be the most important criterion for curative resection. For this reason, patients should be followed routinely with frequent clinical examination and endorectal ultrasonography.

It is important that the same type of tumours are being compared. There are good clinical, technical and pathological reasons for making a distinction between malignant polyps treated by endoscopic polypectomy, large sessile adenomas of the rectum containing a focus of invasive carcinoma treated by local excision, and small ulcerating cancers treated by local resection[22]. Recent progress in preoperative staging has shown the value of endorectal ultrasonography[27–29] to study rectal wall involvement and magnetic resonance imaging to assess regional cancer extension[30]. Clinical examination[31] remains important to appreciate tumour fixity and sphincter involvement. After these investigations, two situations can be considered.

The first concerns low tumours that fit the classical indication for transanal resection, that is they are located within the lowest 10 cm of the rectum, with a diameter less than 3 cm, they do not extend through the rectal wall into the perirectal fat and are characterized by well differentiated grading. Many authors report excellent results for local excision of superficial tumours (*Table 3*): a 3–11 per cent local recurrence rate for stage A tumours[6,8,13,14] and 13–18 per cent for stage B_1[1,12,14]. The 5-year survival rate ranges from 100 to 89 per cent for

Table 3 *Local results and survival after transanal resection with or without postoperative radiotherapy or intracavitary irradiation*

Reference	Year	No. of patients	Tumour stage	Primary treatment	Local recurrence rate (%)	Survival rate (%)	
						3 years	5 years
Grigg *et al.*[6]	1984	16	A*	Transanal resection	6	—	100
Heberer *et al.*[10]	1987	42	A–B_1	Transanal resection	7	—	84
Killingback[11]	1985	28	B_1	Transanal resection	18	—	—
		6	B_2	Transanal resection	33	—	—
Lock *et al.*[12]	1978	22	A–B_1	Transanal resection†	13	—	—
		89	A (pedunculated)	—	6	—	—
Biggers *et al.*[13]	1986	93	*In situ*	Transanal resection	11	95	83
		141	A–B	Transanal resection	27	76	64
Hager *et al.*[14]	1983	39	A	Transanal resection	8	92	89
		20	B_1	Transanal resection†	17	91	78
		36	‡	Transanal resection	24	—	61
Coco *et al.*[8]	1992	32	A–B_1§	Transanal resection plus radiotherapy†	3	—	89
Ramming *et al.*[15]	1986	16	A–B_1	Transanal resection plus radiotherapy	6	100	100
Ellis *et al.*[16]	1988	9	A	Transanal resection plus radiotherapy	0	100	100
Minsky *et al.*[17]	1991	14	A–B	Transanal resection plus radiotherapy	14	—	—
			A	—	0	—	—
			B_1	—	14	—	—
			B_2	—	50	—	—
Bailey *et al.*[18]	1992	53	A–B_1	Transanal resection plus radiotherapy	8	—	90
Papillon[19]	1991	312	A–B_1	Intracavitary irradiation	9	—	92
Papillon and Berard[20]	1992		B_2–C	Radiotherapy plus transanal resection	—	77	—
Sischy *et al.*[21]	1988	94	A–B_1	Intracavitary irradiation	5	—	90

*All tumours possessed a pedicle or pseudopedicle after the application of traction. †Patients with high-grade tumour or incomplete excision were reoperated on early by anterior resection or rectal excision. ‡High-risk tumours: stage B_2, resection line with tumour or undifferentiated carcinoma. §Systematic postoperative radiotherapy (47 Gy) for B_1 tumours

stage A[6,8,14] and from 90 to 78 per cent for stage B_1[10,14] tumours. Papillon[19,32,33] and Papillon and Berard[20] have reported 312 low rectal cancers treated by intracavitary irradiation (stage A–B_1) with an 8·8 per cent local recurrence rate and a 5-year survival rate of 92 per cent. Sischy and associates[21,34] reported equally good results. However, this technique is available at only very few medical centres and does not permit pathological study of the tumour. Whiteway *et al.*[35] perceived local excision as a 'total biopsy' that allowed confirmation of complete removal of the lesion and analysis of other histological parameters. This biopsy could be followed by radical resection, if prognostic factors suggested the need. The 11 per cent failure rate in the present favourable group 1 patients requires consideration. After local excision alone, similar rates have been reported[6,12,13,36], which underlines the need for adjuvant radiotherapy for selected high-risk patients. In the present study, after excision radiotherapy (60 Gy) was given to seven of the 18 patients with small tumours, with good local control in 90 per cent. Like others[16–18,37] we believe that adjuvant postoperative radiotherapy requires 45–60 Gy. When surgical removal was microscopically inadequate, radiotherapy could not compensate for the presence of tumour at the surgical margin. In the present series, disease in three patients with incomplete resection could not be controlled by adjuvant radiotherapy greater than 55 Gy. Rich *et al.*[37] reported a 56 per cent local recurrence rate in nine patients with residual gross disease who received postoperative radiation. Willett *et al.*[25] are alone in reporting no local failures in six patients with pathologically positive resection margins receiving postoperative radiation therapy in whom boost doses were increased to 65 Gy. On the other hand, radiotherapy may decrease the recurrence rate following local excision of early rectal cancer with occult lymph node metastases and/or microscopically unsuspected tumour at the margins[16,18].

The second situation concerns larger and deeper tumours that would ordinarily be treated by APR. Papillon and Berard reported a 5-year disease-free survival rate of 60 per cent and a pelvic failure rate of 7 per cent for T_2 or T_3 low rectal cancer treated by external and endocavitary irradiation[20,32]. In the present small series, a 44 per cent local recurrence rate was found for large tumours (B_1–B_2) with preoperative irradiation of 40 Gy. A 20-Gy postoperative boost reduced the local recurrence rate to 28 per cent. The importance of high-dose preoperative irradiation was outlined by Marks and coworkers[36,38,39]. They reported a 23 per cent local recurrence rate at 3 years and a 61 per cent survival rate for full-thickness local excision after high-dose preoperative irradiation[39]. Local excision after radiotherapy seems to be better than radiotherapy alone, which produced good temporary palliation and initial tumour regression but poor long-term control of disease. The survival rate was often less than 5 per cent. The same authors[36] reported experience of high-dose radiation therapy (60 Gy) followed by curative radical rectal resection and coloanal anastomosis for low and advanced rectal cancer. For favourable post-irradiation stage (0, A, B_1) the local recurrence rate was 0 per cent, and it was 18·3 per cent for unfavourable post-irradiation stage. These excellent results raise the issue of whether local excision is appropriate for favourable post-irradiation stage (0, A), even for an initially fixed and bulky tumour. It implies that the resection margins should be reassessed after preoperative radiotherapy.

Transanal resection should be considered as a curative procedure for selected low, small, well differentiated adenocarcinomas of the rectum. Local control could be improved by postoperative radiotherapy for stage B_1 tumours larger than 3 cm in diameter or for high-grade lesions. Further trials should examine the results of high-dose preoperative radiotherapy to define the role of transanal excision for favourable post-irradiation stages. Curative APR for early local recurrence after transanal resection seems possible when careful follow-up is undertaken.

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Lymph node metastases in early rectal cancer

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Local excision of early rectal tumours is an attractive proposition, avoiding the morbidity and mortality of major resection and possible permanent stoma. This study was designed to investigate the incidence of lymph node metastases associated with tumours that are locally confined to the bowel wall. A total of 454 rectal excision specimens were reviewed. Twenty-two (20 per cent) of 109 patients with tumours locally confined to the bowel wall had metastases in local lymph nodes, although 14 of these had only one or two involved nodes. Three of 27 patients with tumours that did not penetrate through the submucosa had lymph node metastases. Less well differentiated tumours were more likely to have metastasized but there was no significant difference in the height or size of tumours or in the depth of invasion between patients with or without lymph node metastases.

The ideal surgical treatment for potentially curable cancer is removal of all viable tumour cells in a manner that causes the least mortality and morbidity. The usual procedure for rectal cancer is segmental excision of the bowel together with the adjacent mesorectum.

Local removal of carcinoma has been recommended[1–3] as a definitive procedure for early rectal cancer confined to the bowel wall. However, this procedure does not remove local lymph nodes in the mesorectum and thus does not allow full staging of the tumour; nor does it offer the prospect of cure to patients with involved nodes.

This study was designed to define the incidence of metastatic lymph node spread in rectal carcinoma confined locally to the bowel wall and to investigate whether features of the primary tumour may be used to predict nodal involvement. This may allow selection of patients suitable for local excision.

Patients and methods

The histological findings of two consecutive series totalling 454 patients in whom the rectum was removed for cancer were reviewed. These patients were under the care of two surgeons with an interest in colorectal cancer over a 10-year period. In each case the tumour was removed by either a radical anterior approach involving wide mesorectal clearance or by abdominoperineal resection. Patients in whom the local tumour did not penetrate the full thickness of the bowel wall were identified and the presence and number of lymph node metastases sought.

Routine histological preparation was carried out in the hospital laboratory. In one hospital, lymph nodes were identified by a fat clearance technique[4]. In the other hospital, lymph nodes were identified by careful dissection in an attempt to find at least 13 nodes in each specimen. Blocks were not routinely subjected to serial sectioning.

The height of the primary tumour, its diameter, the degree of cellular differentiation and the depth of tumour penetration were studied to determine whether these could be used to predict lymph node metastases. Differentiation was recorded by the reporting pathologist as the least well differentiated area along the invasion margin, assessed by tubule formation, mitotic rate and pleomorphism. Mucoid carcinoma was always classified as poorly differentiated.

Statistical comparison was made between the groups by χ^2 analysis or Student's t test as appropriate. $P < 0.05$ was considered significant.

Results

The 454 tumours in the series comprised 193 (43 per cent) Dukes' C, 174 (38 per cent) Dukes' B and 87 (19 per cent) Dukes' A. The Dukes' A tumours included those from two rectums removed after previous peranal excision of carcinoma confined to the bowel wall in which no further tumour was found in the specimen. There were 109 tumours in which the primary lesion did not extend through the bowel wall. In 22 (20 per cent) of these, metastases were present in local lymph nodes. In the majority (14 of 22) there were only one or two lymph node metastases present, and in only five specimens were more than three nodes involved (*Figure 1*). The tumour in the 22 cases associated with lymph node metastasis extended to the submucosa in three and to the muscularis propria in 19. The depth of invasion and degree of differentiation of tumours that

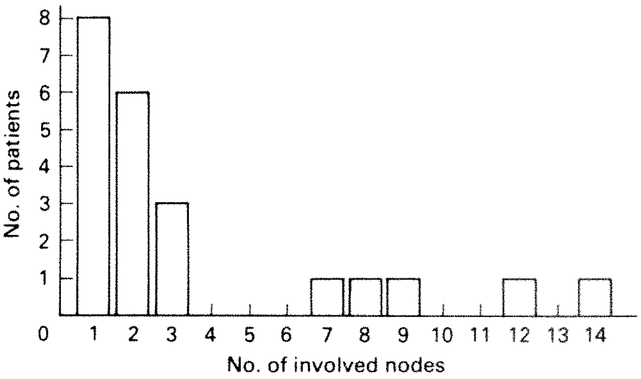

Figure 1 *The number of patients plotted against the number of lymph nodes involved by metastases where the primary tumour did not penetrate the bowel wall*

Table 1 *Depth of tumour penetration and degree of cellular tumour differentiation*

	Node positive ($n = 22$)	Node negative ($n = 87$)
Depth of invasion*		
Limited to submucosa	3	24
Involvement of muscularis propria	19	63
Degree of differentiation†		
Well or moderate	15	77
Poor	7	10

*$\chi^2 = 1.16$, 1 d.f., $P = 0.28$; †$\chi^2 = 4.07$, 1 d.f., $P = 0.044$

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were locally confined to the bowel wall both in patients with and without lymph node metastasis are shown in *Table 1*. Only the degree of tumour differentiation showed a statistically significant difference between the two groups.

The height of the tumour above the anal margin did not differ between the two groups (mean(s.d.) 7·0(3·4) cm for the node-positive *versus* 7·6(3·9) cm for the node-negative group).

Similarly, the diameter of the primary tumour did not differ significantly between the two groups (mean(s.d.) 3·9(1·7) cm for node-positive *versus* 4·2(1·4) cm for node-negative patients).

Discussion

Rectal cancers may be considered in three groups. Tumours penetrating the full thickness of the bowel wall require radical surgery with removal of all local lymph nodes. At the other extreme is a group of tumours that are found in polypectomy specimens, in which the lesion does not involve the base of the stalk, is not poorly differentiated and is not large; in these local removal is probably adequate. This leaves an intermediate group that is considered in this study. The optimum treatment for these tumours is not clear, partly because it is not possible to predict the presence of tumour within local lymph nodes accurately[5,6].

Patients with lymph node metastases and local tumour confined to the bowel wall form a relatively small subgroup (5 per cent in this series) of all those with rectal cancer. This number is comparable to that previously reported by Jass and Love[7]. This group is, however, important as it makes up a significant proportion of patients who may be considered for local removal of cancer and in whom the presence or absence of involved nodes is of crucial importance. Furthermore, the routine techniques used in this study may have underestimated the numbers of involved lymph nodes.

Local removal of rectal tumour is an attractive proposition. The surgery involved is relatively minor with correspondingly low mortality and morbidity rates, and may avoid a temporary or permanent stoma. The technique does not, however, remove mesorectal lymph nodes. Histological examination of these nodes allows staging and an estimation of prognosis. More importantly, removal of metastatic tumour in these nodes in continuity with the primary lesion can frequently be curative, with survival figures[8,9] of over 50 per cent. Furthermore, there is evidence[7] to suggest that patients with Dukes' C tumours in whom the primary lesion does not penetrate the bowel wall have a better prognosis than those with Dukes' C tumours as a whole. Wolmark *et al.*[10] reported fewer involved nodes (mean 2·5 *versus* 4) and more patients with only one involved node (47 *versus* 15 per cent). Copeland *et al.*[11] reported a 47 per cent 5-year mortality rate for this group as opposed to 80 per cent when the tumour penetrated the wall. The operative mortality rate for patients aged less than 70 years undergoing radical surgery is approximately 1 per cent[8]. Clearly, when the involved lymph nodes are left behind, surgery cannot be expected to be curative.

Selection of patients for local removal of tumours of the lower rectum would be easier if it were possible to predict clinically the presence of lymph node metastases. Digital rectal examination has been shown[5] to be an unreliable guide to the presence of local lymph node involvement. Computed tomography is useful in determining the local depth of invasion and the presence of distant metastases, but disappointing in its ability to predict local lymph node involvement[6,12], and little better than digital examination[5]. Transrectal echosonography may prove to be a more useful investigation for the detection of nodal metastases. Beynon *et al.*[12] reported a series of 49 patients with positive nodes with five false-negative investigations. However, the procedure relies on a high degree of expertise and general results are likely to be less satisfactory.

In the present series, lymph node metastases in local lymph nodes were demonstrated in 22 (20 per cent) of 109 tumours locally confined to the bowel wall and in three of 27 when the primary lesion was confined to the submucosa. This is in broad agreement with the results of others. Morson[13] found that 12·1 per cent of patients with tumours that did not penetrate the full thickness of the bowel wall had lymph node metastases, and 10·9 per cent when the tumour was confined to the submucosa.

Small tumour size has been suggested as a criterion for local resection[14]. However, in the present series, when only tumours confined to the bowel wall were investigated, there was no difference in the mean size of tumour with or without associated metastases, and this has also been found by others[11,15]. Larger tumours are, however, more likely to have penetrated the bowel wall. Although poor cellular differentiation was associated with lymph node metastasis, this feature was not determined independently of knowledge of lymph node metastasis, so the possibility of observer bias exists. In any case, the clinical utility of this association is doubtful, as ten of the 17 patients with poorly differentiated tumours did not have nodal metastasis.

Present methods of investigation do not allow accurate prediction of patients who have metastasis to local lymph nodes. Features of the local tumour may provide a guide but are unreliable in the specific case. An early lesion is curable in the majority of cases by adequate surgery. Almost one-fifth of patients will have lymph node metastases and the risks of conservative surgery must be appreciated and taken into account in the planning of optimal treatment for each patient.

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Surgical Research Society Abstracts

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The following abstracts were presented at the 78th meeting of the Surgical Research Society, with Professor L. E. Hughes in the chair. The meeting was held on 8–9 July 1993 at Ninewells Hospital and Medical School, Dundee. One hundred and fifteen papers were presented during the scientific sessions, which were preceded by a symposium entitled 'Tumour biology'. The Patey Prize was awarded to Mr C. Cunningham for his paper entitled 'Deletion mapping in colorectal cancer: sublocalization of a putative tumour suppressor gene on chromosome 8p'.

Tumour blood flow is related to cytotoxic drug uptake

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Vasoactive manipulation to enhance cytotoxic uptake into tumours has been proposed but the underlying assumption that tumour flow correlates with drug uptake has never been tested. This was examined in the present study, which also determined whether angiotensin-induced alteration in blood flow correlates with alteration in 5-fluorouracil (5-FU) uptake.

Nineteen Chester Beatty Hooded rats bearing 183 hooded sarcoma N hepatic tumours underwent a 30-min hepatic artery infusion of saline (nine animals) or angiotensin II (ten). After 25 min a blood flow tracer (copper(II)-pyruvaldehyde *bis*(*n*-4-methylthiosemicarbazone) and tritiated 5-FU were infused. All liver and tumour tissues were counted in γ and liquid scintillation counters to establish blood flow and the 5-FU tumour:liver ratios.

In the saline (control) group there was a high correlation ($r = 0{\cdot}93$, $P < 0{\cdot}0001$) between individual tumour:liver blood flow and 5-FU uptake ratios. Although angiotensin significantly ($P < 0{\cdot}01$) increased the tumour:liver blood flow ratio (median saline 0·13, angiotensin 0·22), there was no significant change in the 5-FU uptake ratio (median saline 0·23, angiotensin 0·27).

Individual tumour variation in blood flow does correlate with 5-FU uptake. However, this relationship does not apply to angiotensin-induced changes in blood flow. This suggests that tumour-related factors are involved in the relationship between tumour blood flow and drug uptake.

Bombesin as a mitogen in human gastric cancer

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Receptors for the mammalian bombesin-like peptides gastrin-releasing peptide (GRP) and neuromedin B (NMB) are found throughout the gastrointestinal tract in the submucosal and myenteric plexuses. They have been demonstrated in human gastric cancer cell lines, but human tumour tissue has not been studied.

The aim of the study was to screen membrane preparations from snap-frozen human gastric cancers and macroscopically uninvolved adjacent mucosa for the presence of bombesin receptors using a standard radioligand displacement assay. ^{125}I-labelled Tyr^4-bombesin was used as radioligand and unlabelled bombesin, GRP and NMB as competitors.

Of 23 gastric cancers, 13 were positive for bombesin receptors whereas no 'normal' gastric mucosa expressed receptors. One patient with Ménétrièr's disease, a recognized premalignant condition, had a bombesin receptor-positive early gastric cancer and bombesin receptor-positive mucosa. Of eight gastric cancers in which the receptor has been subtyped, all expressed the GRP-preferring subtype of the bombesin receptor.

In conclusion, GRP receptors have been demonstrated in 57 per cent of human gastric cancers but not in normal mucosa. The only receptor-positive mucosa was from a patient with disordered mucosal growth. Expression of GRP receptors may be important in the neoplastic transformation of human gastric mucosa. Currently available stable bombesin antagonists may provide a new therapeutic approach to this common human cancer.

Torsion of the testis: a new twist

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Torsion of the testis is a urological emergency. The reported salvage rate is approximately 60 per cent, but as many as two-thirds of these testes subsequently atrophy. Reperfusion injury may explain this delayed testicular loss. The effect of ischaemia and reperfusion on testicular function and structure and the potential protective roles of hypothermia and the anti-ischaemic drug trimetazidine were examined in a rodent model of testicular torsion.

Fifty testes undergoing 3 h of torsion (720°) were divided among seven experimental groups: group 1 ($n = 6$), no reperfusion; group 2 ($n = 6$), 1 h reperfusion; group 3 ($n = 6$), 1 week reperfusion; group 4 ($n = 6$), 1 h reperfusion with hypothermia; group 5 ($n = 6$), reperfusion and hypothermia for 1 h, examined at 1 week; group 6 ($n = 10$), 1 h reperfusion and trimetazidine; and group 7 ($n = 10$), 1 h reperfusion and trimetazidine, examined at 1 week. Mean seminiferous tubular diameter (MSTD), mean tubular wall thickness (MTWT) and the percentage of tubules with spermatozoa were measured. Statistical analysis was performed using Student's unpaired t test.

	1	2	3*	4†	5†	6†	7†
MSTD (μm)	14·6	14·8	12·0	15·0	15·0	15·5	13·4
MTWT (μm)	3·3	3·2	2·1	4·9	4·3	4·6	3·8
Tubules with sperm (%)	84	92	32	96	96	90	3

*$P < 0{\cdot}05$ *versus* groups 1 and 2; †$P < 0{\cdot}05$ *versus* groups 1, 2 and 3

The results show that reperfusion significantly increases testicular injury compared with 3-h torsion alone and is most evident at 1 week. The anti-ischaemic agent trimetazidine given during reperfusion limits testicular injury. Hence, manipulation of reperfusion injury following torsion may limit subsequent testicular atrophy.

Major impairment of bile acid absorption from ileoanal pouches shown by ^{75}Se-HCAT enema scintigraphy

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The enterohepatic circulation of bile acids is crucial for digestion, prevention of gallstones and aspects of intestinal motility. It is unclear whether the mucosal changes that follow ileoanal pouch (IAP) construction affect bile acid absorption (or vice versa). To overcome previous methodological difficulties, bile acid absorption has been examined using a novel technique.

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A 50-ml enema of the radiolabelled bile acid ^{75}Se-HCAT (7 kBq ml^{-1}) and computerized dynamic scintigraphy were used to study bile acid absorption in 15 patients with an IAP (seven with poor pouch function clinically) and in six with an end ileostomy. Log transformation of the absorption curves revealed two components (fast component $t_{1/2}$ 2·8 min; slow component $t_{1/2}$ 49·5 min) in all patients with an ileostomy (six of six), in seven of eight with good pouch function, but in only one of seven with poor pouch function ($2P = 0{\cdot}01$, Fisher's exact test). In the other six patients with poor pouch function there was only one absorption component ($t_{1/2}$ 53 min). ^{75}Se-HCAT absorption in patients with IAP was significantly impaired, and markedly so in those with poor function.

Study group	No. of patients	^{75}Se-HCAT absorption (%)*	
		30 min	60 min
Ileostomy	6	81 (79–87)	—
IAP	15	43 (24–47)	53 (36–70)
IAP (good function)	8	46 (43–53)	65 (57–72)
IAP (poor function)	7	24 (18–38)	36 (24–54)

*Values are median (interquartile range); $P < 0{\cdot}05$ (multiple range tests)

Enema ^{75}Se-HCAT scintigraphy provided remarkably good objective discrimination between IAPs with good and poor function. The role of the non-toxic and easily absorbed bile acid ursodeoxycholate may be worth exploring as oral therapy in patients with pouches with poor function.

Effect of proteinase inhibitors on breast cancer cell invasion

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Proteinases are implicated in the invasion of basement membrane (BM) by breast cancer cells. The roles of various proteinases were studied in an *in vitro* model.

Breast cancer cells were seeded on to [^{35}S]methionine-labelled BM from endothelial cells grown in 96-well plates. After 72 h incubation with and without proteinase inhibitors the percentage of radioactivity released into the culture medium was determined. Oestrogen receptor-negative MDA-MB-231 cells were found to be the most invasive and were used to study the effects of proteinase inhibition.

Pepstatin (cathepsin D inhibitor), E64 (cysteine proteinase inhibitor), aprotinin (a general serine proteinase inhibitor) and BB94, a novel metalloproteinase inhibitor, were used in medium containing 5 per cent fetal calf serum (FCS) or under serum-free conditions. With FCS, pepstatin and E64 produced no significant difference in the degradation of BM, but both aprotinin and BB94 significantly reduced degradation as assessed by one-way analysis of variance (mean(s.d.) proportion of control value: aprotinin 64(22·4) per cent ($n = 13$); BB94 76·1(14·6) per cent ($n = 12$); combined 30(10·3) per cent ($n = 8$)). Under serum-free conditions the aprotinin effect was not found (104·1(12·2) per cent ($n = 6$); $t = 4{\cdot}74$, $P < 0{\cdot}001$ *versus* FCS) whereas BB94 was more effective (41(9·5) per cent ($n = 8$); $t = 6{\cdot}2$, $P < 0{\cdot}001$ *versus* FCS). With FCS, inhibition of plasminogen binding with tranexamic acid (61(12) per cent ($n = 3$)), urokinase-type plasminogen activator (uPA) with specific anticatalytic antibody (47(7·4) per cent ($n = 3$)) and amiloride (57(15) per cent ($n = 4$)) and of plasmin with ε-amino-*n*-caproic acid (62(13) per cent ($n = 3$)) all had a similar effect to aprotinin.

These data suggest that uPA–plasmin and metalloproteinases are the major proteinases involved in breast cancer invasion and offer targets for therapeutic agents.

Tumour-specific monoclonal antibodies induce cytokine release by effector–target cell linkage

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The mechanism of antitumour antibody-dependent cell-mediated cytotoxicity (ADCC) is not well elucidated. The authors have previously suggested that monokines may mediate ADCC by demonstrating that neutralization of tumour necrosis factor (TNF) α produces a partial, but significant, reduction in tumour cell lysis. In this study TNF-α and interleukin (IL) 1β generation was examined during ADCC mediated by the anticolorectal monoclonal antibodies murine 17-1A (m17-1A), chimeric 17-1A (c17-1A) and chimeric SF25 (cSF25). Peripheral blood mononuclear cells were isolated from healthy volunteers, added to the colorectal cell line LS180 and incubated for 18 h with antibody. The supernatant was aspirated and TNF-α and IL-1β levels measured by enzyme-linked immunosorbent assay.

	No antibody	m17-1A	c17-1A	cSF25
IL-1β (pg ml^{-1})				
ET	1080 (382–2000)	1512 (1149–2000)†	1484 (1139–2000)†	2000 (1426–2000)†
E	26 (0–587)*	0 (0–70)*	0 (0–0)*	0 (25–1141)*
TNF-α (pg ml^{-1})				
ET	0 (0–34)	337 (0–2000)‡	436 (157–804)‡	825 (354–1582)‡
E	0 (0–0)	0 (0–0)*	59 (0–73)	7 (0–47)*

Values are median (interquartile range). ET, effectors plus targets; E, effectors alone. $^*P < 0{\cdot}05$ (ET *versus* E); $^†P < 0{\cdot}002$, $^‡P < 0{\cdot}02$ *versus* no antibody (all paired *t* test)

The results show that more TNF-α and IL-1β was detected with m17-1A, c17-1A and cSF25 than without antibody. Combinations of antibody with either effector or target cells alone produced undetectable or low levels. Therefore, only following the union of effectors, targets and antibody is cytokine release induced which may be partially responsible for tumour cell lysis.

Development of less invasive operations for gastro-oesophageal reflux

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Three antireflux operations, fundoplication, gastroplasty and anterior gastropexy, were achieved at flexible endoscopy without laparotomy or laparoscopy. An endoscopic sewing machine mounted on a standard gastroscope, an endoscopic knotting device, over-tube and 0·2-mm diameter nylon threads were used to perform the operations. An anatomical arrangement similar to that of fundoplication was achieved by invaginating the oesophagus and fixing it to the stomach 2 cm distal to the cardio-oesophageal junction. Gastroplasty was accomplished by suturing the anterior and posterior wall of the stomach to create a gastric tube (neo-oesophagus) along the lesser curve. Anterior gastropexy was performed using a technique similar to that used in creating a percutaneous gastrostomy.

Each operation was performed on six beagle dogs. There were no complications. Manometry using a three-channel perfused catheter system before and after the procedure showed a significant increase in the mean lower oesophageal sphincter (LOS) and cardiac yield pressures (mean LOS pressure 4·4 mmHg before operation, 17·6 mmHg after operation; mean yield pressure 10·2 mmHg before operation, 18·0 mmHg after operation).

It is concluded that conventional antireflux operations may be performed at flexible endoscopy without laparoscopy or laparotomy. This study also suggests that a variety of new gastrointestinal surgical operations might be performed 'inside out', i.e. from the mucosal aspect rather than from the traditional surgical approach via the serosal surface.

Successful treatment of severe diabetes mellitus using hybrid artificial pancreas devices

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The application of two types of hybrid artificial pancreas for the treatment of severe diabetes mellitus induced by total pancreatectomy in dogs is reported.

The intravascular device consists of a coiled ultrafiltration membrane (nominal molecular weight cut-off 80 kDa), surrounded by an annular islet chamber and anastomosed to the iliac vessels. The intraperitoneal device consists of multiple tubular (2–4 cm × 5 mm) membrane diffusion chambers ('straws') fabricated from the same membrane.

A single intravascular device was unable to control blood sugar levels consistently. In a series of double-device implants involving 65 dogs, control of the blood sugar level was achieved for between 1 and 9 months in 70 per cent of dogs and for 1 year in two animals. Device removal resulted in a rapid increase in the fasting blood sugar level and exogenous insulin requirement (>30 units per day) ($P<0\cdot001$).

Six dogs received straws. Three did not require any exogenous insulin for >50 days, with <10 units per day for >100 days. Failure was attributed to membrane fracture and islet isolation problems.

Metabolic studies, postexplant *in vitro* studies and histological analyses confirmed islet cell survival and insulin production. There was no rejection.

These hybrid artificial pancreas devices have a clear clinical potential for islet cell transplantation without immunosuppression.

Double-blind randomized controlled trial of dietary calcium supplementation in individuals with adenomas

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Dietary supplementation with calcium reduces rectal mucosal proliferation in individuals at high risk of colorectal cancer. However, there have been few long-term randomized controlled trials in individuals with sporadic adenomas.

A total of 138 individuals (age range 34–70 years) underwent colonoscopy, were found to have adenomas and offered dietary supplementation. Seventy-nine patients accepted and were entered into a double-blind randomized controlled trial of 1500 mg calcium per day or placebo.

Mucosal proliferation (crypt cell production rate (CCPR)) was measured by the *in vitro* metaphase arrest technique.

Four individuals withdrew from the study in the first 12 months.

	CCPR (cells per crypt per h)		
	0 months	3 months	12 months
Calcium ($n=40$)	12·2(5·5)	9·0(2·8)*	9·3(3·3)†
Placebo ($n=39$)	10·6(5·2)	9·4(2·9)	8·9(3·3)

Values are mean(s.d.). *$t=3\cdot15$, 76 d.f., $P=0\cdot002$ (3 *versus* 0 months); †$t=2\cdot7$, 74 d.f., $P=0\cdot009$ (12 *versus* 0 months)

There were no significant changes in proliferation in the control group. Supplementation with 1500 mg calcium produced a sustained reduction in rectal mucosal proliferation, even after 12 months.

It is too early to comment on the effect of calcium on new adenoma formation. However, there appears to be a role for dietary supplementation of calcium in larger and longer cancer prevention trials.

Effect of the surgeon's specialty interest on resection specimen lengths in surgery for colorectal cancer

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A number of studies have demonstrated a surgeon-related variability in patient outcome following surgery for colorectal cancer. The aim of this study was to determine whether there is a correlation between the length of the formalin-fixed resection specimen and the surgeon's specialty interest. Three surgical groups were identified: surgeons with an interest in colorectal cancer (CCI), those with an interest in gastroenterology (GII) and those with a specialty interest other than CCI or GII (OSI). Over a 1-year period 158 colectomies were performed; 125 were thought to be curative.

Resection lengths and margins for right-sided cancers were similar in each group. Median (range) resection lengths for curative left-sided colonic and rectal cancers for each group were:

Specialty interest	Resection length (mm)*
OSI ($n=21$)	130 (87·5–180)
GII ($n=19$)	200 (150–220)
CCI ($n=41$)	280 (220–320)

*Medians are highly significantly different (Kruskal–Wallis test)

Distal resection margins (30 mm) were similar for rectal cancer in all groups. However, for sigmoid cancer the median distal resection margin was 20 mm in groups GII and OSI compared with 55 mm in group CCI ($P=0\cdot001$). This study demonstrates a wide variability in the type of resection performed for left-sided colonic and rectal cancer by surgeons with different specialty interests. Prospective studies evaluating patient outcome in relation to surgical interest and type of resection are required.

Haemodynamic changes associated with colorectal liver metastases: evidence of a humoral mediator

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Splanchnic haemodynamic derangement, including reduced portal venous inflow, appears to be one of the earliest manifestations of liver metastasis in colorectal cancer. To investigate the hypothesis that this is humorally mediated, splanchnic vasoconstrictor activity was assessed in plasma from rats with intrahepatic hooded sarcoma N tumour (group 1), in patients with overt colorectal liver metastases (group 2) and in patients with colorectal cancer without overt metastases but with abnormal haemodynamics as assessed by duplex ultrasonography (group 3) (Doppler perfusion index (DPI; ratio of hepatic artery:total liver blood flow) $>0\cdot30$), a high-risk group for early hepatic relapse. Respective control groups were sham-operated rats, patients with no cancer and patients with colorectal cancer but with no overt metastases and with normal haemodynamics (DPI $<0\cdot30$).

Paired experimental and control plasma samples (100 μl) were injected intra-arterially in rat small bowel preparations, vascularly perfused with oxygenated Krebs' solution (5·5 ml min^{-1}). Response was measured as the peak increase in perfusion pressure. Rat samples were retested after blockade of α-adrenergic, vasopressin, angiotensin II, 5-hydroxytryptamine$_2$ and P2$_x$-purinergic receptors and neural conduction.

Group	*n*	Response (%)*	*P*†
1 (tumour-bearing rats)	18	118(4)	<0·005
1 (in blocked preparation)	18	135(211)	<0·01
2 (overt metastases)	9	188(26)	<0·01
3 (abnormal haemodynamics)	16	120(7)	<0·05

*Values are mean(s.e.m.) percentage of control. †Wilcoxon test

This study provides the first direct evidence that prognostic haemodynamic changes in patients with colorectal cancer are associated with a humoral vasoconstrictor. This is unlikely to be one of the major circulating constrictor hormones, and could be a marker for occult liver metastasis.

Expression of cripto and amphiregulin in the prognosis of rectal cancer

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Cripto and amphiregulin (AR) are two newly discovered members of the epidermal growth factor family. The aim of this study was to assess the expression of AR and cripto in rectal cancer and its relationship to prognosis.

Two 17-mer synthetic peptides corresponding to the *C*-termini in the human cripto and AR proteins were used to generate monospecific antisera in rabbits. Paraffin-embedded sections were stained by the avidin–biotin complex immunoperoxidase technique using polyclonal anticripto and anti-AR antibodies.

Of 58 rectal carcinomas, 53 (91 per cent) stained for AR and 41 (71 per cent) for cripto. Cripto was expressed more in tumours of the lower third of the rectum ($P<0\cdot005$) and in flat–excavated tumours ($P<0\cdot01$). Of 54 samples of normal mucosa adjacent to the tumour, 20 (37 per cent) were positive for cripto. Ten of these 20 expressed more cripto than the tumour and all had cancer recurrence and bowel wall penetration. High cripto immunoreactivity in the normal mucosa correlates with nodal involvement ($P<0\cdot01$).

In conclusion, high levels of AR and cripto expression are frequently found in rectal tumours. High cripto immunoreactivity in the normal mucosa adjacent to the tumour correlates with tumour recurrence. Further studies are in progress to validate the use of cripto as a prognostic marker in patients with rectal cancer.

Prevalence of anal intraepithelial neoplasia in renal allograft recipients

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An increase in the prevalence and incidence of human papilloma virus (HPV)-associated genital intraepithelial and invasive neoplasia occurs in immunosuppressed organ transplant recipients. Although a similar trend has been suggested for the aetiologically related anal squamous neoplasia, there have been no studies of the prevalence of anal squamous neoplasia in recipients of organ transplants. The present study tested the hypothesis that renal transplant recipients have a higher risk of intraepithelial neoplasia of the anus than control patients of a similar age.

Ninety-eight renal transplant recipients (59 men, mean age 45·6 years; 39 women, mean age 47·8 years) were recruited and underwent anal colposcopy. A histological diagnosis of anal intraepithelial neoplasia (AIN), including one case of anal cancer, was made in 24 per cent of the study group. The distribution of the lesions is shown.

	Men	Women	Total
AIN I	13	6	19
AIN II	0	2	2
AIN III	1	1	2
Anal cancer	0	1	1

HPV 16 DNA was identified in anal biopsies in 30 (42 per cent) of 72 patients in the study group. No evidence of AIN was found in the control group (50 women, 20 men). HPV 16 DNA was identified in seven anal biopsies (10 per cent) in the control group.

The results suggest that the prevalence of AIN is higher in renal transplant recipients than in controls. The need for anal examination in screening for AIN in these patients requires further investigation.

Swainsonine inhibits colorectal cancer tumour cell invasion *in vitro*

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Swainsonine, a plant alkaloid, inhibits murine tumour metastasis *in vivo*. Swainsonine has not been studied as an anti-invasive agent in human colorectal tumours. The human colorectal cancer cell line SW620 was cultured *in vitro* for 4 days with or without $10\,\mu g\,ml^{-1}$ swainsonine. Cells were plated on to basement membrane (Matrigel)-coated filters in double-chamber cassettes. Tumour cells invading from upper to lower chambers were counted. At 6 h after plating, swainsonine reduced cell migration on to lower chamber filters from 19·1 to a mean(s.d.) 8·4(2·5) cells per field ($n = 11$; $P < 0·01$, paired t test).

To determine whether swainsonine modified cell adhesion to Matrigel, SW620 cells were cultured for 4 days with varying concentrations of swainsonine and coated on to 96-well plates. After 1 h, non-adherent cells were removed and the remaining cells fixed, stained and counted.

	Swainsonine concentration ($\mu g\,ml^{-1}$)				
	0	1	2	5	10
No. of cells ($\times 10^3$ per well)	14·9(1·3)	10·9(2·3)*	11·4(1·7)*	9·4(1·7)*	10·8(2·0)*

Values are mean(s.d.) of 15 samples. $P < 0·001$ (one-way analysis of variance); *$P < 0·01$ versus control (Duncan's post-analysis of variance comparison)

It is concluded that swainsonine inhibits basement membrane invasion by tumour cells *in vitro*; this may be attributable to inhibition of tumour cell adherence to the membrane. This study indicates the need for further investigation of swainsonine as an antimetastatic agent.

Cytokines and signalling pathways controlling a cancer–stromal paracrine loop in breast cancer

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There is speculation that breast cancer cells and stromal fibroblasts participate in a positive feedback loop of paracrine growth stimulation. The putative growth factors controlling this loop have been investigated using human breast fibroblasts and the breast cancer cell line MCF-7.

Fractionation of serum-free fibroblast-conditioned medium (FCM) demonstrated a mitogen of approximately 8 kDa, inactivated by trypsin and dithiothreitol and non-heparin binding, which excludes the fibroblast growth factors. Activity was not inhibited by neutralizing antibodies to epidermal growth factor, transforming growth factor α or the insulin-like growth factor 1 receptor, eliminating the common non-heparin-binding mitogens. Treatment of MCF-7 cells with FCM resulted in tyrosine phosphorylation of specific cellular proteins demonstrated by Western blotting, suggesting a mechanism of signal transduction.

MCF-7-conditioned medium (CCM) was mitogenic for fibroblasts. Treatment of fibroblasts with either CCM or platelet-derived growth factor (PDGF) resulted in a transient rise in the intracellular calcium level, measured by dual-wavelength fluorimetry with the indicator Fura-2. CCM mitogenicity was inhibited by a neutralizing antibody to PDGF.

The results clearly show that PDGF released by breast cancer cells stimulates the growth of fibroblasts which, in response, release an 8-kDa peptide that is mitogenic for cancer cells.

Cyclosporin A-induced fibroadenomas: a model for tumour genesis

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Multiple bilateral fibroadenomas are uncommon. The finding of four cases in women who had received renal transplants prompted further enquiry. A prospective study was performed on 39 women under the age of 55 years who had received a renal transplant at least 1 year earlier. Clinical examination was performed by an experienced clinician and breast ultrasonography by an experienced radiologist. Factors considered included immunosuppressive treatment, steroids, renal function, diuretics, calcium channel and H_2-receptor blockers. Blood was taken for estimation of serum creatinine levels and hormone profiles. Fibroadenomas, generally multiple and bilateral, were found in 13 of the 39 patients. The mean(s.d.) serum oestradiol concentration in women with fibroadenomas was higher than in those without (569(162) *versus* 283(61) $pmol\,l^{-1}$).

In patients who had received cyclosporin A, 12 of 28 had fibroadenomas, compared with only one of 11 of those who had not ($\chi^2 = 4·05$, $P < 0·05$). The presence of gingival hypertrophy, a recognized side-effect of cyclosporin A therapy, did not correlate with the presence of fibroadenomas (six of 12 with fibroadenomas, seven of 16 without). There was no association between the presence of fibroadenomas and use of steroids, azathioprine or any other medication.

It is concluded that cyclosporin A induces the development of multiple breast fibroadenomas. Cyclosporin has an *in vitro* effect on fibroblast growth, which may be modulated *in vivo* by an increase in serum oestradiol, as is suggested by this study.

Investigation of a novel pure antioestrogen in women with primary breast cancer

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Tamoxifen is the antioestrogen of choice for the treatment of breast cancer but exhibits agonist activity, which may reduce its efficacy. The tolerance and short-term biological effects of ICI 182 780 (182), a novel pure oestrogen antagonist, have been investigated in postmenopausal women with primary breast cancer. Fifty-six patients were randomized to either a control group (19 patients) who received no preoperative treatment or a treatment group (37) who received daily intramuscular injections of 182 at doses of 6 mg (21 patients) or 18 mg (16) for 7 days before surgery. The expression of oestrogen receptor (ER), progesterone receptor (PR) and the proliferation-related antigen Ki67 was determined immunocytochemically in tumour samples taken before and after treatment. Serum gonadotrophin and sex hormone-binding globulin (SHBG) levels were measured by radioimmunoassay. Ethical committee approval for the study was obtained.

182 caused no serious drug-related adverse events and had no effect on serum gonadotrophin or SHBG levels. Expression of ER, PR and Ki67 was significantly reduced in ER-positive tumours after therapy with 182, but there were no significant changes in ER-negative or control tumours.

	Control		ICI 182 780	
	Before	After	Before	After
ER	35	60	45	3·5*
PR	38	60	30	0·5*
Ki67	3·7	3·4	3·2	1·1*

Values are median percentage of cells stained before and after treatment. *$P<0{\cdot}05$ *versus* before treatment (Wilcoxon matched-pairs signed rank test)

In conclusion, 182 is well tolerated during short-term administration and produces antioestrogenic effects in human breast tumours *in vivo*, with no evidence of agonist activity.

Chemotherapy–radiotherapy and L-arginine: clinical and pathological responses in patients with breast cancer

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L-arginine increases the synthesis of human breast tumour protein and the number of tumour cells in the growth phase of the cell cycle. Thus, it may potentiate the anticancer response to cell cycle-specific cytotoxic agents. This pilot study assessed clinical and pathological responses to neoadjuvant chemotherapy–radiotherapy in patients with breast cancer supplemented with L-arginine.

Forty-four patients with breast cancer (T_2, seven patients; T_3, 21; T_4, 18) received oral L-arginine (30 g day^{-1} for 3 days) before each cycle of combination chemotherapy, and then proceeded to radiotherapy. Following chemotherapy 92 per cent of patients achieved a clinical response: complete response in 22 per cent and partial response in 70 per cent (Union Internacional Contra la Cancrum criteria). The overall clinical response rate increased to 95 per cent following radiotherapy, and ultrasonography and mammography revealed response rates of 91 and 76 per cent respectively. Surgery was performed in 44 patients (mastectomy, 28; quadrantectomy, 16). Pathology specimens were graded I–IV: (I) changes in tumour cells but tumour nests not destroyed; (II–IV) mild, moderate and severe destruction of tumour structure; and (V) no tumour cells present. Results were: grade I, one patient; II, seven; III, 13; IV, 15; and V, eight (complete response rate 18 per cent).

These results suggest that L-arginine is able to potentiate clinical and pathological responses to chemotherapy–radiotherapy.

pLiv1: an oestrogen-regulated gene associated with lymph node involvement in breast cancer

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Oestrogen receptor (ER) status is an established prognostic marker in breast cancer. However, not all ER-positive tumours respond to endocrine therapy and this may be due to a non-functional receptor in some cancers. Several oestrogen-regulated genes have been cloned and investigated as better markers of a functional ER. The expression of two such genes, pLiv1 and pS2, has been examined in 74 patients with primary breast cancer.

The results show that pLiv1 and pS2 are expressed almost exclusively in ER-positive tumours, although they are not invariably coexpressed. Considering all 74 patients, pLiv1, but not pS2, expression correlated with lymph node involvement ($P<0{\cdot}01$). With ER-positive tumours alone, pLiv1 expression was even more strongly associated with nodal disease: 15 of 18 ER-positive pLiv1$^+$ tumours were node positive while 20 of 23 ER-positive pLiv1$^-$ tumours were node negative ($P<0{\cdot}001$). This association was further strengthened when small ER-positive tumours (<2 cm) alone were considered: 11 of 12 node-positive tumours were pLiv1$^+$ and 17 of 22 node-negative ones were pLiv1$^-$. pLiv1 expression did not correlate with tumour size or lymphovascular invasion.

In conclusion, pLiv1 is a candidate gene for metastatic spread in ER-positive breast cancer.

Quantitative polymerase chain reaction assay for pNR-2–pS2 messenger RNA in fine-needle aspirates from breast tumours

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Because of the poor predictive value of oestrogen receptor (ER) status alone in assessing the endocrine responsiveness of breast tumours, the use of reverse transcription and the polymerase chain reaction (PCR) in the measurement of pNR-2–pS2 messenger RNA (mRNA) in fine-needle aspirates is described. This assay uses reverse transcription and PCR amplification of aliquots of cellular RNA, extracted using guanidinium thiocyanate and quantified by spectrophotometry.

Before reverse transcription, a known quantity of synthetic mutated pNR-2–pS2 RNA is added to each aliquot. The mutation generates a recognition site for BamH1 enzyme digestion which is found centrally in the PCR target sequence. Digestion of the PCR products with BamH1 cuts the product of mutant origin, leaving the product of cellular origin intact. The products can be distinguished by differential migration on gel electrophoresis and quantified by ethidium bromide staining and gel scanning.

pNR-2–pS2 mRNA levels, measured in 0·1 μg cell-line RNA, were:

	MCF-7	EFM-19	T47-D	MDA-MB-231
Oestrogen responsive	Yes	Yes	Yes	No
pNR-2–pS2 mRNA (pg per μg total RNA)	715	433	14	Not detectable

These levels are comparable to those obtained by hybridization. In a preliminary study, usable RNA was obtained from seven of ten fine-needle aspirates from mastectomy specimens. pNR-2–pS2 mRNA was assayed using 1 μg. The results were:

	1	2	3	4	5	6	7
pNR-2–pS2 mRNA (pg per μg total RNA)	15·0	4·8	3·0	2·6	n.d.	n.d.	n.d.
ER concentration (fmol per mg total protein)	313	n.d.	368	4·4	2·4	0·4	—

n.d., Not detectable

This assay may be useful in predicting the responsiveness of breast cancer to primary tamoxifen therapy.

Influence of pneumoperitoneum on lower-limb haemodynamics

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The scope of laparoscopic surgery is increasing. Prolonged pneumoperitoneum may have adverse pathophysiological effects. Recent reports have suggested an associated increased incidence of thromboembolic disorder.

Lower-limb venous haemodynamics were studied in 40 patients (25 women, 15 men; median age 52 years) undergoing laparoscopic cholecystectomy. Half were randomized to wear graduated compression stockings during operation, and half wore no stockings. Standardized venous capacitance (VC) and venous outflow (VO) were measured non-invasively before, during and after induction of pneumoperitoneum.

In the group without stockings, VC and VO scores decreased during pneumoperitoneum in 65 per cent of patients, returning to previous levels on release of the pneumoperitoneum. In contrast, in 90 per cent of the patients with stockings, scores remained at preoperative levels or rose once pneumoperitoneum had been established. There was a significant difference in standardized median VC and VO values at mid-operation between the two groups for both legs:

Group	VC	VO
Stockings		
Left leg	1·29(1·02)	1·36(1·21)
Right leg	1·26(1·26)	1·26(1·29)
No stockings		
Left leg	0·82(0·52)*	0·82(0·52)†
Right leg	0·83(0·60)†	0·83(0·60)†

Values are median(interquartile range). $^*P = 0·001$; $^†P < 0·001$ *versus* stockings (Mann–Whitney *U* test)

Pneumoperitoneum creates a significant resistance to venous return from the lower limbs. Compression stockings counteract the observed changes.

Neutrophil degranulation produced by experimental venous hypertension

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Neutrophil activation may cause skin damage in patients with chronic venous insufficiency. Two experimental models of venous hypertension were used: a thigh tourniquet inflated to 80 mmHg for 30 min and standing for 30 min.

Twelve normal volunteers (nine men, three women; mean age 31 years) were investigated. Cannulas (18 Fr) were placed in veins of both feet and of the right hand, and blood samples taken before and after the two periods of hypertension, separated by a 30-min rest period. Blood was taken for neutrophil count and estimation of the plasma lactoferrin level, a secondary granule enzyme that was used as a marker of neutrophil activation, measured using an enzyme-linked immunosorbent assay.

	Tourniquet		Standing	
	Before	After	Before	After
Lactoferrin (ng ml^{-1})*	221·5 (153–238)	248 (188·5–299·5)†	230 (179·5–349)	276·5 (201·5–420)‡

*Values are median (interquartile range). $^†P = 0·028$ *versus* before tourniquet (Wilcoxon test; difference between medians 39 (95 per cent confidence interval (c.i.) 10·5–91) ng ml^{-1}); $^‡P = 0·0009$ *versus* before standing (Wilcoxon test; difference between medians 45·5 (95 per cent c.i. 26·5–66) ng ml^{-1})

There was a significant rise in the plasma lactoferrin level compared with the baseline value in both models of venous hypertension. Short-term venous hypertension causes neutrophil activation in normal subjects.

Free radical-induced lipid peroxidation in carotid endarterectomy

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Reperfusion of ischaemic tissues can cause cellular damage by lipid peroxidation with the release of by-products such as malondialdehyde (MDA) and diene conjugates (DCs). This study investigated the occurrence of lipid peroxidation during carotid endarterectomy.

In 24 patients undergoing this operation, blood samples for plasma MDA and DCs were obtained from the jugular vein at the start of surgery, just before the application of carotid clamps during shunting, and at 30, 60, 120, 180 and 300 s after the clamps were released. Carotid clamp times were recorded.

Significant increases in mean(s.e.m.) concentrations of MDA and DCs were observed at 60 s after clamp release (MDA 559(64) pmol ml^{-1}, DCs 428(32) units ml^{-1}) compared with those at the beginning of surgery (MDA 408(34) pmol ml^{-1}, $P < 0·01$; DCs 374(28) units ml^{-1}, $P < 0·05$). A significant correlation was observed between the percentage rise in MDA concentration and clamp time ($r = 0·45$, $P = 0·03$).

These results suggest that clamping of the carotid artery leads to lipid peroxidation, which may adversely influence outcome in patients undergoing carotid endarterectomy and possibly in other situations of transient cerebral hypoperfusion.

Microvascular constriction follows skeletal muscle ischaemia–reperfusion and is associated with reduced endothelial capacity to mediate vessel dilatation

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Arteriolar vasoconstriction and spasm have been postulated to contribute to no-reflow following ischaemia–reperfusion and so add to tissue injury. This work investigated skeletal muscle microvascular response to ischaemia–reperfusion using direct *in vivo* microscopy in a paired (CD-1) mouse cremaster model. Arteriolar diameters (30–80 μm) were measured before and after a 6-h period of complete ischaemia. In other groups, the effect of topical acetylcholine (10^{-4} mol l^{-1}) and nitroprusside (10^{-5} mol l^{-1}) treatment were compared with topical saline alone. One muscle was rendered ischaemic, while the contralateral muscle served as a non-ischaemic control (six animals in each group).

Results showed diameter changes 15–30 min after starting reperfusion. Topical saline had no significant effect on arteriolar diameter.

	Arteriolar diameter		
	Postreperfusion	Acetylcholine	Nitroprusside
No ischaemia	89(7)	104(4)*	103(3)*
Ischaemia–reperfusion	55(9)	65(8)	84(5)*

Values are mean(s.e.m.) percentage of preischaemic diameter. $^*P < 0·05$ *versus* saline (paired *t* test)

In conclusion, significant vasoconstriction ($P < 0·05$) followed ischaemia–reperfusion in this model. The ability of nitroprusside to induce vessel dilatation indicates that extrinsic nitric oxide-mediated smooth muscle relaxation was preserved, while the failure of acetylcholine to cause dilatation indicates impaired endothelium-dependent (intrinsic nitric oxide-mediated) vasodilatation. Loss of critical local (nitric oxide-dependent) influences on dilatation may therefore contribute to reperfusion-induced microvascular constriction.

Thromboxane antagonism prevents hindlimb ischaemia–reperfusion-induced gut damage

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Thromboxane released on reperfusion of ischaemic tissue may promote intestinal permeability causing endotoxin absorption and multiorgan failure. The effect of the thromboxane receptor antagonist ICI 192 605 on the penetration of horseradish peroxidase (HRP) beyond the tight junctions of ileal enterocytes, and on the absorption of mannitol from the bowel into the portal circulation, was studied in anaesthetized rats in two experiments of four groups.

	HRP permeability		
Group	Negative	Positive	Mannitol (mg l^{-1})*
1 (ischaemia)	6	0	15·1(4·1)
2 (reperfusion)	0	6	36·2(8·1)
3 (DMSO)	2	4	34·2(4·6)
4 (antagonist)	6	0†	16·4(3·5)‡

*Values are mean(s.d.). $^†P < 0·05$ *versus* group 2 (Fisher's exact test); $^‡P < 0·05$ *versus* group 2 (analysis of variance)

Group 1 underwent a 5-h period of hindlimb ischaemia, and groups 2–4 underwent 3 h hindlimb ischaemia and 2 h reperfusion. During the period of reperfusion, an infusion of dimethyl sulphoxide (DMSO) was given to animals in group 3 and an infusion of ICI 192 605 in the solvent DMSO to those in group 4. Groups receiving HRP contained six rats and the groups given mannitol contained ten.

Thromboxane receptor antagonism prevents the abnormal permeability that follows hindlimb ischaemia and reperfusion.

Nitric oxide attenuates revascularization-induced lung injury

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Limb revascularization following aortic occlusion leads to lung injury dependent on activated neutrophil adherence. Nitric oxide inhibits neutrophil aggregation and adherence to endothelial cells. To determine *in vivo* whether nitric oxide has a role in attenuating ischaemia–reperfusion-induced lung injury, the effect of increasing or decreasing nitric oxide levels with sodium nitroprusside (SNP) or *N*-nitro-L-arginine methyl ester (L-NAME) respectively was evaluated in an aortic occlusion–lung injury model of 30-min ischaemia and 2-h reperfusion.

Sprague–Dawley rats (ten per group) were randomized to controls, ischaemia–reperfusion, ischaemia–reperfusion treated with L-NAME (10 mg kg^{-1}) and ischaemia–reperfusion treated with SNP (0·4 mg kg^{-1}) during reperfusion. Myeloperoxidase (MPO) activity measured pulmonary neutrophil influx. Pulmonary endothelial permeability was measured by wet:dry weight and bronchoalveolar lavage protein (BAL protein) and neutrophil counts (BAL PMN).

	Control	Ischaemia–reperfusion	L-NAME	SNP
Wet:dry weight	3·15(0·05)	4·08(0·9)*	5·9(0·4)‡	2·8(0·2)§
MPO (units g^{-1})	3·05(0·4)	6·1(0·1)†	8·9(0·7)‡	3·5(0·4)‡
BAL protein (mg)	347(32)	454(16)*	581(40)§	330(61)
BAL PMN	0·7(0·05)	1·8(0·07)†	2·7(0·16)‡	0·9(0·1)§

Values are mean(s.e.m.). $^*P < 0·05$, $†P < 0·001$ *versus* control; $‡P < 0·05$, $§P < 0·001$ *versus* ischaemia–reperfusion (all unpaired Student's *t* test)

A significant increase in MPO activity and microvascular leakage was produced by ischaemia–reperfusion, which was exacerbated further by administration of L-NAME. SNP therapy attenuated the ischaemia–reperfusion-induced lung injury. These data suggest that nitric oxide *in vivo* inhibits ischaemia–reperfusion-induced lung injury, perhaps by inhibiting pulmonary neutrophil influx.

Deletion mapping in colorectal cancer: sublocalization of a putative tumour suppressor gene on chromosome 8p

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Several genetic events are implicated in colorectal carcinogenesis. Abnormalities of tumour suppressor genes p53 (chromosome 17p), *APC* (5q) and *DCC* (18q), in addition to activating mutations in the K-*ras* oncogene, are frequent occurrences. Results that indicate a novel tumour suppressor gene locus on the short arm of chromosome 8 are reported.

Allele loss studies were performed using polymorphic chromosome 8 markers comparing 120 tumour and matched normal DNA samples.

Some 52 per cent of tumours showed allele loss with chromosome 8p markers which were independent of deletions at chromosomes 5q and 17p. No correlation was noted between allele loss of 8p markers and site or stage of the tumour, or the sex or age of the patient at diagnosis.

The use of high-density markers allowed sublocalization of the region of interest. Six tumours were identified with crucial breakpoints indicating that the tumour suppressor gene locus on chromosome 8p lies between the ankyrin 1 and lipoprotein lipase genes, a region of approximately 30 cM.

These findings indicate a small target region for molecular cloning and eventual isolation of the putative tumour suppressor gene.

Luminal adrenergic agents modulate ileal transport by activation of α_1 and α_2 receptors

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Luminal α-adrenergic agonists alter ileal transport. This study tested the hypothesis that luminal α-adrenergic agents modulate ileal transport selectively, via specific α_1 and α_2 receptors.

Absorption studies ($n = 63$) were performed on dogs with 25-cm ileal Thiry–Vella fistulas. Perfusion with [^{14}C]polyethylene glycol was used to calculate absorption of water, ions and glucose from the fistula. Experiments included four 1-h periods: basal, α-antagonist infusion, α-antagonist with and without α-agonist infusion, and recovery. Agonists used were phenylephrine (PHE; α_1), clonidine (CLON; α_2) and noradrenaline (NA; $\alpha_1 > \alpha_2$). Antagonists were terazosin (TZ; α_1) and yohimbine (YOH; α_2). All adrenergic agents were delivered luminally at 10^{-4} mol l^{-1}.

The agonists PHE and NA caused significant increases in water and ion absorption, while CLON caused significant decreases in water, ion and glucose absorption. The antagonists TZ and YOH had no effect alone. TZ prevented the proabsorptive effect of PHE and NA. YOH increased the NA-induced proabsorptive effect. Data are expressed as the integrated water absorption (ΔA) for hours 3 and 4, compared with hour 2:

Infusion*	ΔA water
PHE	+10·7(6·0)†
PHE plus TZ	−2·1(4·5)
CLON	−11·8(8·2)†
CLON plus YOH	−7·4(8·0)†
NA	+11·3(6·6)†
NA plus TZ	+1·9(2·2)
NA plus YOH	+21·3(5·5)†

Values are mean(s.e.m.). *Nine animals were used for each infusion. +, Increased absorption; −, decreased absorption. $†P < 0·05$ *versus* hour 2 (analysis of variance)

Ion absorption paralleled water absorption. In conclusion, α_1-receptor activation causes a proabsorptive response for water and ions, while α_2 activation causes a prosecretory response for water, ions and glucose. The combination of a luminal α agonist (NA) with α_2 blockade may prove useful in pathological secretory states such as intestinal transplants or diarrhoea-associated endocrinopathies.

Breast cancer mortality in carriers of the *BRCA1* gene mutation is significantly lower than that in the general population

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Female carriers of the *BRCA1* gene mutation have a lifetime risk of breast cancer >80 per cent. To investigate whether breast cancer survival in *BRCA1* carriers is different from that in the general population, DNA from 35 women with breast cancer was typed using polymorphic markers D17S588 and D17S579 on chromosome 17q12-21 in eight breast cancer pedigrees with a high probability of linkage to *BRCA1* (range 79·2–99·9 per cent). Genetic typing suggested that all women had linkage to the *BRCA1* mutation.

The 5-year survival rate in *BRCA1* carriers was 83 per cent (24 of 29 individuals). In an age-matched control population, the 5-year survival rate was significantly lower at 61·1 per cent (556 of 910 individuals) ($\chi^2 = 4·70$, $P < 0·05$). In contrast, the 5-year survival rate in women from seven breast cancer pedigrees not obviously linked to *BRCA1* (probability of linkage range 41·1–63·5 per cent) was 59 per cent, similar to that in an age-matched population (59·2 per cent).

It is unlikely that *BRCA1*-linked pedigrees are preselected to favour prolonged survival. Furthermore, epidemiological data do not suggest an earlier stage of disease at presentation in women with strong family history of breast malignancy.

In conclusion, predisposition to breast cancer with prolonged survival may be a phenotypic effect of the *BRCA1* mutation.

Glutamine-supplemented total parenteral nutrition improves T cell response in surgical patients

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Many *in vitro* studies have demonstrated potential benefits of glutamine on T cell function, but T cell response after glutamine administration to patients is unknown. Glutamine is unstable and is not contained in conventional total parenteral nutrition (TPN). As the dipeptide, it is stable and is rapidly hydrolysed *in vivo* to the amino acid form. This prospective study evaluated the effect of glutamine dipeptide supplementation of TPN on the T cell response and on production of the proinflammatory cytokines interleukin (IL) 6 and tumour necrosis factor (TNF) from peripheral blood mononuclear cells (PBMCs) of patients with cancer undergoing colorectal resection.

Twenty patients were randomized to either conventional TPN (0·2 g nitrogen $\text{kg}^{-1}\,\text{day}^{-1}$) or an isocaloric, isonitrogenous regimen containing 0·18 g glutamine $\text{kg}^{-1}\,\text{day}^{-1}$ from days 1–6 after operation. *Ex vivo* peripheral blood T cell response (DNA synthesis on blastogenic stimulation) and IL-6 and TNF production from endotoxin-stimulated PBMCs were determined before surgery and on days 1 and 6 after operation.

	T cell response	PBMC TNF	PBMC IL-6
Glutamine			
Pre-TPN (day 1)	90 (64–105)	129 (51–201)	167 (103–221)
Post-TPN (day 6)	137 (105–166)*‡	182 (131–263)*	108 (85–131)
Control			
Pre-TPN (day 1)	88 (69–124)	146 (69–293)	176 (85–264)
Post-TPN (day 6)	108 (77–129)	179 (89–228)†	107 (72–149)

Values are median (interquartile range) percentages of the preoperative value. *$P=0{\cdot}02$, †$P=0{\cdot}03$ *versus* preoperative value (paired Wilcoxon test); ‡$P=0{\cdot}03$ *versus* control (Tukey–Duckworth test)

Glutamine supplementation significantly improved T cell response without altering production of IL-6 or TNF. It may be a method of enhancing T cell function in the immunocompromised patient receiving TPN.

Cytokines, the acute-phase response and resting energy expenditure in patients with pancreatic cancer

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Patients with pancreatic cancer frequently lose weight. Anorexia is a recognized phenomenon in these patients, but the role of a raised energy expenditure and the acute-phase response remains more controversial.

Twenty-four patients with pancreatic cancer who were losing weight and 17 controls underwent measurement of resting energy expenditure (REE) by indirect calorimetry and of body cell mass (BCM) by bioelectrical impedance analysis. The REE of patients with cancer was significantly raised compared with that in controls (72·5(4·4) *versus* 54·1(1·6) kcal per kg BCM per 24 h; $P<0{\cdot}002$). The association of REE to the systemic inflammatory response in patients with cancer was assessed by measurement of serum C-reactive protein (CRP), tumour necrosis factor (TNF) and interleukin (IL) 6 levels and the production of IL-6 and TNF by isolated peripheral blood mononuclear cells (PBMCs).

	CRP $\leqslant 10\,\text{mg}\,\text{l}^{-1}$ ($n=13$)	CRP $>10\,\text{mg}\,\text{l}^{-1}$ ($n=11$)	P*
REE (kcal per kg BCM per 24 h)	64·2(2·7)	82·1(8·1)	0·0406
Serum TNF (pg ml^{-1})	n.d.	n.d.	—
Serum IL-6 (pg ml^{-1})	102(10)	169(56)	0·22
PBMC TNF (pg per ml per 10^5 cells)	210(55)	1193(240)	0·0003
PBMC IL-6 (ng per ml per 10^5 cells)	3·4(1·3)	11·7(1·4)	0·0003

Values are mean(s.e.m.). n.d., Not detectable. *Student's unpaired t test

Of patients with pancreatic cancer 46 per cent had a systemic inflammatory response (CRP $>10\,\text{mg}\,\text{l}^{-1}$). These patients had a significantly raised REE compared with those without an inflammatory response and they also had significantly increased rates of cytokine production by PBMCs. Such patients might benefit from treatment with agents that attenuate the inflammatory response.

Calcipotriol inhibits rectal epithelial cell proliferation in ulcerative colitis

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Vitamin D reduces human rectal crypt cell production rate (CCPR) and may protect against colorectal cancer by reducing cell proliferation. Cell turnover is also increased in ulcerative proctocolitis, which might therefore respond to vitamin D metabolites. The effect of calcipotriol, a synthetic vitamin D analogue that avoids hypercalcaemia, on human rectal CCPR in ulcerative proctocolitis was investigated.

Paired rectal biopsies from seven patients with severe disease were established in organ culture with or without calcipotriol ($1\times10^{-6}\,\text{mol}\,\text{l}^{-1}$). After 15 h, vincristine ($0{\cdot}6\,\mu\text{g}\,\text{ml}^{-1}$) was added to induce metaphase arrest, and the CCPR was determined by linear regression analysis of accumulated metaphases.

Compared with values in 17 controls with incidental anal conditions, the median (range) rectal CCPR was 28 per cent higher in patients with ulcerative proctocolitis (5·90 (2·85–7·07) *versus* 4·80 (5·00–9·50) cells per crypt per h, $P<0{\cdot}01$). Calcipotriol reduced the mean(s.e.m.) CCPR by 69 per cent in patients with ulcerative proctocolitis, from 6·58(0·78) to 2·06(0·36) cells per crypt per h ($P<0{\cdot}001$).

Thus, calcipotriol can dampen the hyperproliferative state in ulcerative proctocolitis and could have a therapeutic role in the control of this inflammatory condition.

Glutathione S transferase μ gene deletion is a significant risk factor for transitional cell carcinoma of the bladder

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The major risk factors for development of transitional cell carcinoma (TCC) of the bladder are smoking and occupational exposure to chemicals. These risks may be modified according to genetic host factors. The enzyme glutathione S transferase μ (GSTM1) acts by detoxifying reactive intermediate compounds, for example benzo(*a*)pyrene-4,5 oxide. GSTM1 is polymorphic and 50 per cent of the population lacks the gene coding for this enzyme. The hypothesis was that GSTM1 gene deletion is a significant risk factor in TCC.

Using a polymerase chain reaction-based restriction fragment length polymorphism technique, genomic DNA was analysed in 53 patients with proven TCC of the bladder. DNA from 52 age-matched controls undergoing transurethral resection of the prostate and that from 58 healthy volunteers was also analysed. Some 46 per cent of healthy volunteers and 40 per cent of patient controls were positive for GSTM1. Of 53 patients with bladder cancer, eight (15 per cent) were GSTM1 positive, fewer than in the two control groups ($\chi^2=8{\cdot}41$, $P<0{\cdot}005$ for patient controls; $\chi^2=12{\cdot}67$, $P<0{\cdot}001$ for healthy controls). A relative risk of 1·42 (95 per cent confidence interval (c.i.) 1·12–1·79) with an odds ratio of 3·81 (95 per cent c.i. 1·53–9·34) was found for gene deletion.

The enzyme GSTM1 may have a protective role in the development of TCC.

Oesophageal squamous cell carcinoma: prediction of response to chemoradiotherapy

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Up to 30 per cent of patients with a squamous tumour of the oesophagus will undergo complete regression following combined chemoradiotherapy. The ability to predict responders from pretreatment biopsy specimens would have obvious advantages. Epidermal growth factor receptor (EGFR) overexpression in oesophageal squamous cell carcinoma has been shown to be associated with a poor outcome; its role in predicting response to treatment has not been explored. Proliferating cell nuclear antigen (PCNA) is a cell-proliferating associated nuclear protein.

Biopsy material was taken endoscopically before treatment from 14 patients undergoing chemoradiotherapy (cisplatin, 5-fluorouracil and 40-Gy radiotherapy) before surgery. At subsequent oesophagectomy, six patients had no residual tumour (group 1) while eight had persistent tumour (group 2). Formalin-fixed paraffin-processed biopsy material taken from each patient before treatment was analysed histologically for tumour grade and immunocytochemically stained using monoclonal antibody to EGFR and PCNA. The proliferation index and EGFR expression for each tumour were assessed.

Tumour grade was a poor predictor of response to therapy. The mean PCNA index was lower in responders than in non-responders (25 *versus* 42 per cent), but there was considerable overlap (P not significant). In contrast, all the non-responders showed intense staining for EGFR, while five of six responders were negative ($P = 0{\cdot}003$, Fisher's exact test).

The results indicate that EGFR expression may be a useful indicator of patient response to combined chemoradiotherapy for oesophageal squamous carcinoma.

Smoking in patients with periductal mastitis and duct ectasia

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It is not clear whether the clinical syndrome of periductal mastitis (PDM), which is characterized by periareolar inflammation with or without nipple discharge and/or retraction, and its complications, non-lactating breast abscess and mammary duct fistula, and the clinical syndrome of duct ectasia (DE), characterized by nipple discharge, crusting of the nipple, nipple retraction and non-inflammatory periareolar mass, are related or separate conditions. The present study looked at the incidence of smoking and previous benign breast disease in the two conditions.

A prospective study of 14 322 patients presenting over a 4-year period is summarized. Patients with PDM and DE were compared with an age-matched group.

Clinical diagnosis	No. of patients	Smokers (%)	Previous benign disease (%)	Median age (years)
PDM	68	88*	47*	33
Non-lactating abscess	39	87*	71*	35
Mammary duct fistula	32	94*	100*	31
DE	186	24†	28†	58

*$P < 0{\cdot}0001$, †P not significant (*versus* age-matched controls without PDM)

The same findings for smoking are true when the analysis is restricted to patients who have histologically proven PDM or DE. Previous benign disease in patients with PDM was almost exclusively inflammatory episodes, compared with a single inflammatory episode in the DE group. PDM and DE are separate conditions with different aetiologies.

Interaction of vitamin D and parathyroid hormone-related protein in patients with breast cancer

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Serum vitamin D ($1{,}25(OH)_2D$) has previously been shown to be suppressed in hypercalcaemia of malignancy (HM). However, animal studies have suggested that parathyroid hormone-related protein (PTHrP), the putative cause of HM, stimulates $1{,}25(OH)_2D$ synthesis.

The aim of this study was to measure serum $1{,}25(OH)_2D$ and plasma PTHrP concentrations in three groups of patients with breast cancer: those with early breast cancer (EBC; 27 patients), breast cancer bone metastases (BM; 11) and hypercalcaemia of malignancy (HM; 11). Plasma PTHrP levels were measured using a two-site immunoradiometric assay (normocalcaemic controls, PTHrP $< 0{\cdot}23$ pmol l^{-1}). Serum $1{,}25(OH)_2D$ was measured using an inhouse radioimmunoassay (normal range 20–50 pg ml^{-1}).

In normocalcaemic patients with EBC and in those with BM plasma PTHrP was undetectable. In patients with HM, however, eight of nine had raised PTHrP levels (mean 3·51 (range $< 0{\cdot}23$–20·74) pmol l^{-1}). Serum $1{,}25(OH)_2D$ levels were higher in patients with EBC (mean 47 (range 22–71) pg ml^{-1}) than in those with BM (mean 34 (range 12–76) pg ml^{-1}). Sequential levels at monthly intervals were shown to fall in five patients with BM ($P = 0{\cdot}059$). In patients with HM, all $1{,}25(OH)_2D$ serum levels were low (mean 16 (range 5–29) pg ml^{-1}).

In summary, the serum $1{,}25(OH)_2D$ level falls as breast cancer progresses and this is associated with an increase in plasma PTHrP concentration. These results indicate that PTHrP does not stimulate $1{,}25(OH)_2D$. The progressive action of PTHrP on bone resorption and renal tubular reabsorption of calcium may lead to inhibition of renal 1-α hydroxylase, with the onset of hypercalcaemia.

Screen-detected prevalent breast cancer: axillary dissection is necessary

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The results of first-round screening over 3 years in a mammography screening programme were assessed. The objective of the study was to measure parameters in patients found to be node positive or negative to analyse whether axillary dissection is necessary in all cases.

Eighty-four cancers were detected. Twenty-one patients had positive nodes on level II axillary clearance and 63 had no nodal involvement. Nodal blocks deemed negative on initial haematoxylin and eosin staining were stained with monoclonal antibody to epidermal membrane antigen to detect micrometastases. Some 8 per cent of node-negative patients were found to have micrometastatic disease. Differences in tumour size, grade and type between node-negative and node-positive groups were assessed.

	Node-positive patients (%)	Node-negative patients (%)
Tumour grade		
I	5	3
II	20	54
III	75	43
Tumour size (cm)		
< 1	5	16
1–2	25	43
2–3	35	35
3–4	10	3
> 4	25	3

There were no characteristics of the primary tumours, taken either separately or in combination, that could accurately predict the presence of nodal metastases or micrometastases. It is therefore recommended that axillary clearance is necessary in all patients with prevalent cancer detected by mammographic screening.

Preliminary evaluation of a combined optical–Doppler ultrasonographic instrument for the detection of breast cancer

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The use of a combined optical–Doppler ultrasonographic technique was evaluated in the detection of breast carcinoma. Light absorption (TDDU), determined by the number of blood cells per unit volume of breast, results in the detection of an opaque lesion, and subsequent Doppler ultrasonography detects neovascularization at the periphery of the tumour.

In total, 189 patients (147 symptomatic, 42 attending breast screening) were investigated (mean age 54 years). In only two cases was TDDU considered undiagnostic (compared with 11 mammograms, seven in very dense breasts); cysts showed as translucent areas but fibroadenomas and other benign lesions not associated with neovascularization were not detected.

There were 97 neoplastic lesions. The sensitivity and specificity were: light scanning, 74 and 90 per cent; and mammography 99 and 90 per cent respectively. TDDU was less sensitive for small and impalpable tumours and did not detect ductal carcinoma *in situ* (26 false negatives; mean(s.d.) diameter 1·1(0·3) cm). Subsequent Doppler ultrasonography did not further increase the sensitivity of the examination. Patients with locally advanced breast cancer showed significant changes on repeated optical–Doppler examination, in concordance with the clinical response documented following neoadjuvant chemotherapy.

The combined optical–Doppler instrument, with its low sensitivity, is not suitable for screening, even in the young dense breast, but may have a role in assessing the response of large tumours to chemotherapy.

Screening mammography: prospective evaluation of a combined mammographic and cytological scoring system

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Stereotactic localization and fine-needle aspiration cytology (FNAC) has a role in the management of non-palpable breast abnormalities. As part of a regional breast screening programme the mammograms of more than 18 000 patients with no palpable breast lesion were scored 1–5 by two radiologists; 208 patients whose mammogram scored in the range 3–5 had localization biopsies and prior stereotactic cytological assessment.

The cytological smears were scored as benign (grade 1), acellular (2), atypical (3), suspicious (4) and malignant (5) by an independent cytologist. A combined score was thus generated. This study evaluated its potential in the management of screen-detected abnormalities.

Of 96 malignant lesions, 70 were correctly diagnosed by cytology. The sensitivity (85 per cent), specificity (98 per cent) and positive predictive value (99 per cent) of grade 4 or 5 cytology results compared favourably with those of other series. Significantly, all 60 patients with combined mammographic and cytology scores $\leqslant 4$ had true benign disease following excision biopsy and all 40 with a combined score $\geqslant 8$ had malignancy.

Repeat mammography rather than excision biopsy can now be recommended for patients with a mammography–cytology score $\leqslant 4$ and primary wide local excision for those with a score $\geqslant 8$.

Comparison of the effects of relaxation and befriending on anxiety reduction in patients with breast cancer

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Initial findings are presented from an ongoing longitudinal study to measure the effects of two psychological interventions on reducing anxiety in patients with breast cancer.

Sixteen patients were randomized to receive either relaxation (taught by volunteers), befriending (by nurses trained in psychotherapy) or the current level of care (control).

A battery of questionnaires was administered to all patients before operation and at fixed intervals afterwards. These questionnaires included the Hospital Anxiety and Depression (HAD) and the Mental Adjustment to Cancer (MAC) scales.

For all patients the therapeutic interventions showed no group effects on anxiety (HAD) at the postoperative level. However, for 19 patients who reported severe anxiety (>10) before operation, relaxation produced a significant reduction ($P=0{\cdot}02$) in anxiety at 3 and 6 months after surgery compared with control values.

In addition, for all patients the type of surgery had more effect in reducing anxiety between the preoperative and postoperative stages. Patients undergoing mastectomy showed a greater reduction in anxiety than those having partial mastectomy ($P<0{\cdot}009$). Those receiving relaxation also had a significant reduction in their fatalism (MAC) score ($P=0{\cdot}01$).

It is concluded that: (1) relaxation produces beneficial effects after operation in patients reporting severe preoperative anxiety; and (2) the type of surgery has a more immediate effect than psychological intervention in reducing initial levels of anxiety.

Axillary node status provides additional prognostic information

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Axillary node status is accepted as the best prognostic factor in breast cancer. Many surgeons only sample nodes and thus miss important prognostic information. The prognostic value of full axillary node clearance performed on 540 women undergoing mastectomy for early breast cancer, with a minimum of 10 years' follow-up, was compared with that of 16 different standard prognostic factors.

Tumour grade and size, menopausal status, number of positive nodes (NPN), level of axillary nodal involvement (ANL), node-positive ratio (NPR) and the Nottingham Prognostic Index (NPI) ($P<0{\cdot}001$) were all univariately predictive of survival. Multivariate analysis revealed that only NPR, ANL, NPN, grade and menopausal status remained significant. For node-positive patients, only NPN, ANL, NPR and tumour size provided independent prognostic information.

Factor	Univariate P (χ^2 test)	Cox multivariate analysis z	Cox multivariate analysis P
ANL	$<0{\cdot}001$	3·33	$<0{\cdot}005$
Tumour size	$<0{\cdot}009$	2·92	$<0{\cdot}005$
Tumour grade	$<0{\cdot}02$	2·91	$<0{\cdot}013$
Menopausal status	$<0{\cdot}02$	2·48	$<0{\cdot}01$
NPN	$<0{\cdot}001$	2·44	0·17
NPR	$<0{\cdot}001$	2·42	0·16

A new index based on ANL, NPN and NPR detected four groups of patients; the 10-year survival rate was 93 per cent (group 1, $n=62$), 69 per cent (group 2, $n=176$), 46 per cent (group 3, $n=114$) and 6 per cent (group 4, $n=60$). Prognostic indices that utilize node sampling data (e.g. the NPI) provide poor discrimination compared with those utilizing full axillary node clearance.

Tissue polypeptide-specific antigen: a new serum marker of proliferative activity in breast cancer

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Serum tumour markers have been widely investigated in breast cancer. Current tumour markers reflect tumour bulk, and this unit has reported on the use of some of these in managing metastatic disease. Tissue polypeptide-specific antigen (TPS) is a novel serum marker in that it has been shown to reflect cell proliferative activity, rather than bulk, for a range of solid tumours. Few studies have evaluated TPS as a marker in breast cancer.

TPS was assayed in serum from 19 normal subjects and from patients with stage I and II (19), stage III (20) and stage IV (20) breast cancer before therapy. Mean (95 per cent confidence interval) serum TPS levels were: normals 76·69 (56–97), stage I and II 92·26 (61–122), stage III 217·58 (73–361) and stage IV 1183·75 (615–1752) units l^{-1}. Patients with stage IV disease had a significantly higher level of TPS than those with stage I–III disease, with no overlap of confidence intervals ($P<0{\cdot}001$, analysis of variance with range testing).

In stage IV disease, the serum TPS level showed no correlation with the site of metastases, response to endocrine therapy, duration of response or survival from metastases.

In conclusion, serum TPS assay is a useful indicator of metastatic spread in breast cancer.

Essential fatty acids inhibit breast cancer growth *in vivo*

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Manipulation of fats in experimental breast cancer has produced conflicting results. Individual fats may be more important than overall quantity. Essential fatty acids (EFAs) of the n-6 series are metabolized abnormally in malignant cells and profoundly alter human breast cell proliferation *in vitro*. Their effect *in vivo* is unknown.

The effect of the n-6 EFA γ-linolenic acid (GLA) on xenografted human breast cancer growth in nude mice was examined.

Three groups of 22 female athymic mice (MF1 *nu/nu*01A) were inoculated with 2×10^6 fibroblasts and 2×10^6 MCF-7 human breast cancer cells in the right hind mammary fat pad. GLA suspended in 1 per cent Tween-80 at doses of 200 and 400 mg kg^{-1} was administered daily by intraperitoneal injection. Control animals received 1 per cent Tween-80. After 5 weeks the animals were killed, tumours weighed and examined histologically.

Three deaths occurred from infective complications. Fewer tumours were retrieved from the treated animals than from controls (six of 21 in the 200 mg kg^{-1} group, seven of 20 in the 400 mg kg^{-1} group *versus* 19 of 22 in the control group) ($P<0\cdot001$, χ^2 test). The median (interquartile range) tumour weight in controls (195·5 (35·5–252·0) mg) was significantly greater than that in treated animals (0 (0–52·0) and 0 (0–53·8) mg for the 200 and 400 mg kg^{-1} groups respectively) ($2P<0\cdot01$ and $<0\cdot001$ respectively, Mann–Whitney U test).

Systemic administration of GLA significantly reduces the growth of xenografted human breast cancer in athymic mice.

Water and electrolyte absorption is not altered by small bowel autotransplantation

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The absorptive abilities of transplanted small intestine are not well documented. A model that eliminates the confounding factors of rejection, ischaemia and reperfusion, and that retains portal venous drainage, was used to study water and electrolyte absorption in both the jejunum and ileum.

An 80-cm isolated loop was created in four groups of six dogs that had: neurally intact jejunum (group 1), 'autotransplanted' jejunum (group 2), neurally intact ileum (group 3) and 'autotransplanted' ileum (group 4). Dogs were studied 1, 2, 8 and 9 weeks after operation. The loops were perfused with a solution of 150 mmol l^{-1} sodium chloride at 3 ml min^{-1} for 3 h. Each dog was studied on three separate occasions at each of the four time points.

Net absorptive fluxes for water, and for sodium and chloride (data not shown) were similar ($P>0\cdot05$) in neurally intact and autotransplanted animals in both the jejunum and ileum, and at all time points, despite the autotransplanted dogs having severe diarrhoea for the duration of the study. The normal physiological pattern of the ileum absorbing more than the jejunum ($P<0\cdot02$) was retained in the autotransplants.

	Net absorptive flux of water ($\mu\text{l cm}^{-1}\text{ min}^{-1}$)			
Week	Group 1	Group 2	Group 3	Group 4
1	6·3(0·5)	4·1(2·0)	13·0(1·5)	13·8(2·0)
2	6·2(0·8)	7·0(0·8)	11·2(1·2)	12·4(1·1)
8	4·4(1·2)	5·4(1·4)	11·3(1·4)	11·0(1·4)
9	4·5(0·8)	5·4(1·1)	9·8(1·2)	11·8(1·9)

Values are mean(s.e.m.)

The denervation resulting from small intestinal transplantation does not alter basic water and electrolyte absorption. Patients with an uncomplicated small bowel transplant should have the ability to absorb clear fluids 1 week after operation.

Preferences for decision making in women newly diagnosed with breast cancer

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This study examined women's wishes with regard to involvement in decision making when breast cancer had been diagnosed.

Some 150 women with early breast cancer were compared with 200 with benign breast disease. Five cards, representing all levels of involvement in decision making from the completely active through collaboration to the completely passive, were shown to the subjects in randomly ordered pairs. Using Coomb's unfolding theory, 57 per cent of women with breast cancer were shown to have preference orders that fell on to a single psychological dimension of keep, share or give away control. Of patients with breast cancer, 52 per cent wanted a passive role, with 13 per cent wanting the most passive order. In the benign group, a second dimension was found in 39 per cent of women in the order share, keep or give away control. Overall, newly diagnosed subjects wanted to play a passive role while those with benign disease were more likely to want to play a collaborative role (46 per cent).

Patients with breast cancer were offered an active role in the decision-making process but 61 per cent of the subjects believed they had played a passive role. Comparing the actual role with the desired one, 38 per cent of patients had what they wanted, 39 per cent wanted a more active role and 23 per cent to be more passive.

Quality of life after renal transplantation: surgical perspective

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Transplantation is the ideal renal replacement therapy, but is quality of life really improved? Surgeons have been slow to address this issue. A prospective study of quality of life before and after transplantation was undertaken.

The Nottingham Health Profile (NHP) is a self-completion questionnaire measuring perceived health. Part I covers distress in six areas of daily living: energy, emotional reactions, social isolation, sleep, physical mobility and pain. Part II covers seven aspects of living that are most affected by ill health: occupation, looking after the home, social, home and sex life, hobbies and holidays.

The NHP was completed by 145 potential recipients awaiting a cytotoxic crossmatch (91 underwent transplantation, 54 continued dialysis) and again at 3 and 12 months. Demographic details and initial NHP scores were similar in both groups.

Scores for energy, emotional reactions and social isolation were improved at 3 and 12 months compared with pretransplant values ($P<0\cdot01$, Wilcoxon test), as were all aspects in part II ($P<0\cdot01$, McNemar test). In the dialysis group, higher scores were found at 12 months for all areas in part I compared with initial scores ($P<0\cdot01$), but with no difference in part II responses.

Quality of life is improved by successful renal transplantation, while deteriorating with time on dialysis. Efforts to increase transplantation rates need to be pursued.

Cyclosporin, nifedipine and gingival hyperplasia: a randomized controlled study

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Gingival hyperplasia is a common and distressing side-effect of cyclosporin A (CsA) therapy, with reported incidences of 7–80 per cent. It has been linked in this context with nifedipine, a calcium-channel blocker, frequently used in transplantation for control of hypertension. The incidence of gingival hyperplasia was studied within the framework of a randomized trial comparing three immunosuppressive regimens, with nifedipine treatment in one arm.

At transplantation, patients were randomized to receive either high-dose CsA and prednisolone (group 1), high-dose CsA, prednisolone and nifedipine (group 2) or low-dose CsA, prednisolone and azathioprine (group 3). Assessment of gingival hyperplasia was made 3 months after transplantation and graded as none, mild, moderate or severe. Edentulous patients do not develop gingival hyperplasia and were excluded from the analysis.

Group	No. of patients	None or mild	Moderate or severe
1	15	15	0
2	17	8	9*
3	17	14	3

$^*P<0\cdot001$ *versus* groups 1 and 3

Results showed that patients in group 2 were at significantly higher risk of developing gingival hyperplasia than those in groups 1 or 3.

This study confirms that the combination of high-dose CsA and nifedipine predisposes to gingival hyperplasia. Importantly, there have been reports of malignancy arising within areas of gingival hyperplasia, in a group of patients already at high risk of *de novo* cancer.

Effect of low-dose dopamine on bowel mucosa oxygenation in aortic surgery

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It has been proposed that dopamine, given in low doses, improves mesenteric blood flow. The effect of administering dopamine at a rate of $3\,\mu g\,kg^{-1}\,min^{-1}$ on the intramucosal pH (pH$_i$) of the sigmoid colon was examined in patients undergoing elective abdominal aortic aneurysm repair. pH$_i$ was measured tonometrically. The development of intramucosal acidosis is a reliable indicator of bowel ischaemia.

Nineteen patients were randomized into two groups, one of which received dopamine. Nine of the 19 patients were given dopamine, commencing at induction of anaesthesia and continued for 24 h. The mean(s.e.m.) urinary output was significantly higher in those who received dopamine than in those who did not (3·1(0·4) *versus* 2·1(0·2) litres, $P<0\cdot05$). The mean(s.e.m.) pH$_i$ was significantly lower in the dopamine group than in the other group (6·85(0·10) *versus* 7·09(0·07), $P<0\cdot05$). Five of the nine patients in the dopamine group developed intramucosal acidosis compared with only one of the ten in the other group ($P=0\cdot06$).

These results indicate that dopamine did not have a beneficial effect on oxygenation of the bowel mucosa in this group of patients. Its use to improve mesenteric blood flow in this situation should be further evaluated as it may have significant deleterious effects.

Cyclosporin-induced renal vasoconstriction is due in part to nitric oxide substrate depletion

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Cyclosporin A (CsA) causes intrarenal vasoconstriction, which may account for its nephrotoxic effects. Nitric oxide (NO) is produced by vascular endothelial cells and protects the microcirculation during other vasoconstrictive states. In this study *in vivo* microscopy was used to investigate the role of NO in maintaining renal vascular tone and in protecting against CsA-induced vasoconstriction.

Hydronephrotic kidneys, in decerebrate rats, were suspended in an environmentally controlled tissue bath with neurovascular supply intact. Arteriolar diameters and flow in the interlobular artery (ILA), afferent arteriole (AFF) and efferent arteriole (EFF) were measured by videomicroscopy and Doppler velocimetry. Measurements were made at baseline and 15-min intervals following addition of CsA to the bath. In study groups ($n=6$), L-arginine (L-Arg), a NO substrate, or *Nω*-nitro-L-arginine methyl ester (L-NAME), a NO antagonist, were added to the bath.

	Saline	CsA	L-Arg	L-NAME	CsA plus L-Arg	CsA plus L-NAME
ILA diameter	−1(1)	−20(2)*	7(5)	−14(3)*	−8(4)†	−18(2)*
ILA flow	−1(3)	−66(4)*	4(9)	−39(7)*	−23(8)†	−61(6)*
AFF diameter	5(1)	−20(2)*	11(5)*	−19(6)*	−9(4)†	−23(5)*
EFF diameter	1(2)	−15(2)*	12(3)*	−5(6)	−8(4)†	−18(6)*

Values are mean(s.e.m.) percentage increase or decrease (−) from the baseline at 60 min. *$P<0\cdot05$ *versus* saline; †$P<0\cdot05$ *versus* CsA alone (analysis of variance)

CsA-induced vasoconstriction was significantly reduced by the addition of L-Arg. Inhibition of NO by L-NAME constricted preglomerular vessels but had no further effect on CsA-induced vasoconstriction. NO plays a significant role in maintaining renal vascular tone. Inadequate substrate may limit the NO counter-regulatory dilator response to CsA-induced vasoconstriction.

Induction of heat-shock proteins in transplanted human liver

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The heat-shock or stress proteins (HSPs) are cytoprotective agents that are known to be induced by noxious stimuli. Transplanted organs are subjected to such insults during preservation and reperfusion. Changes in the expression of inducible HSP 70 during routine liver transplant procedures were assessed.

Tru-cut liver biopsies were taken before and after hepatic reperfusion from 30 adult livers transplanted into 28 recipients. Total RNA was extracted and reverse transcribed. Complementary DNA (cDNA) was amplified by a novel semiquantitative polymerase chain reaction technique using primers specific for HSP 70 and β-actin (internal standard) and incorporating [^{32}P]2′-deoxyadenosine 5′-triphosphate. Results were expressed as the ratio of HSP 70:β-actin products.

RNA was reverse transcribed successfully from 26 sample pairs. Comparison of HSP 70:β-actin product ratios revealed a significant induction of HSP 70 with a median increase of 63 per cent ($P<0\cdot05$, Wilcoxon matched-pairs signed rank test).

	Before reperfusion ($n=26$)	After reperfusion ($n=26$)
HSP 70:β-actin ratio	0·74 (0·23–2·33)	1·24 (0·40–3·08)

Values are median (interquartile range)

This novel technique allows the determination of changes in gene expression using small surgical biopsies. Using this method induction of the potentially cytoprotective protein HSP 70 following hepatic reperfusion has been described.

Depletion of Langerhans' cells in renal allograft recipients: a possible factor in cutaneous neoplasia

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Cutaneous squamous cell carcinoma (SCC) is the commonest neoplastic lesion following renal transplantation. It is well documented that patients are also at increased risk of viral and other skin infections. Although a failure of immunosurveillance has been postulated as the cause of the increased level of cutaneous infection, little evidence exists to support this concept. The aim of this study was to investigate the distribution of Langerhans' cells (LCs) (cutaneous antigen-presenting cells) in renal allograft recipients with SCC and in matched controls.

Punch biopsies from non-lesional skin of renal allograft recipients with SCC, control allograft patients, healthy controls and control subjects with SCC were studied using an immunoperoxidase method employing antibodies against LCs. The skin sections were assessed semiquantitatively (graded 0–4) by two independent observers.

	LCs	
	Epidermis	Dermis
Allograft plus SCC ($n=15$)	2 (1–3)	0 (0–1)
Control allograft ($n=24$)	2 (1–3)	0 (0–1)
Controls plus SCC ($n=15$)	3 (3–3)	1 (1–1)
Healthy controls ($n=8$)	3 (3–4)	1 (1–1)

Values are median (interquartile range)

There were significantly fewer LCs in the skin of renal allograft recipients in all layers studied ($P<0\cdot005$, Mann–Whitney *U* test) and many recipients demonstrated virtually total depletion. There was no difference between subjects with or without SCC in either transplant or non-transplant groups.

The severe depletion of LCs in allograft recipients may be a major factor in the development of neoplastic skin disease.

Provision of back-up arteriovenous fistulas in patients receiving continuous ambulatory peritoneal dialysis

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Arteriovenous fistulas (AVFs) are provided for patients undergoing continuous ambulatory peritoneal dialysis (CAPD) as a 'back-up' to allow emergency haemodialysis during episodes of severe peritonitis or CAPD failure from other causes. Of AVFs performed in the authors' unit last year 53 per cent were back-ups, representing a significant financial and time cost in terms of surgical workload.

A preliminary survey confirmed that 42 per cent of renal units in the UK currently have a policy for providing patients receiving CAPD with back-up AVFs.

An audit was made of 176 patients who started CAPD between 1986 and 1989. Over a median follow-up period of 4 years the majority of patients (73 per cent) did not require haemodialysis.

Of the 153 back-up fistulas formed in 114 patients, only ten were ever used for emergency haemodialysis. Twenty-three other patients required emergency haemodialysis but, when required, their fistulas were no longer functioning. Mean fistula patency times in this study compare favourably with those of other published series, with 1- and 3-year rates of 73 and 60 per cent respectively.

This study has shown that the need for emergency haemodialysis has been overstated. When it is required, most fistulas are not available; 94 per cent of fistulas were never used for haemodialysis. We consider that it is no longer justifiable to provide back-up fistulas in patients undergoing CAPD.

Anti-Epstein–Barr virus monoclonal antibody prophylaxis of post-transplantation lymphoma

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Opportunistic Epstein–Barr virus (EBV) infection is implicated in the pathogenesis of B cell lymphoma (BCL) complicating immunosuppression in transplant recipients. Inhibition of EBV infection may prevent BCL. Severe combined immunodeficient (SCID) mice develop BCL when engrafted with human peripheral blood leucocytes (PBLs) and infected with EBV. This model was employed to assess the ability of an anti-EBV-specific monoclonal antibody (MAb) THP-5, which inhibits EBV entry into susceptible B cells, to delay or prevent development of BCL.

SCID mice were engrafted by intraperitoneal inoculation of 50×10^6 PBLs preincubated with THP-5 (5 or 50 μg per ml protein) or control murine immunoglobulin (Ig) G (50 $\mu\text{g ml}^{-1}$) and infected by intraperitoneal inoculation of 5×10^3 transforming units of EBV. Mice were observed for tumour development and killed when weight loss ≥ 40 per cent occurred with palpable abdominal masses. The day of death was taken as the endpoint for each assay.

Engraftment–infection	Category	*n*	Mortality rate (%)	Death after engraftment–infection (days)*
PBLs (no EBV)	Negative control	10	0	—
PBLs plus EBV	Positive control	10	100	31 (27–40)
PBLs plus EBV plus IgG	MAb control (group 1)	10	100	55 (48–79)†
PBLs plus EBV plus THP-5	MAb (5 $\mu\text{g ml}^{-1}$) (group 2)	10	100	77 (55–101)‡
PBLs plus EBV plus THP-5	MAb (50 $\mu\text{g ml}^{-1}$) (group 3)	10	80	83 (63–114)§

*Values are median (range). †$P<0{\cdot}05$ *versus* group 2; ‡$P<0{\cdot}05$ *versus* group 3; §$P<0{\cdot}01$ *versus* group 1 (all log rank test)

In addition to the implications for the pathogenesis of post-transplantation lymphoma, these data suggest that MAbs protective against EBV infection may prove beneficial for the prophylaxis and treatment of this and other EBV-associated disorders in the expanding population of immunosuppressed solid-organ transplant recipients.

Cultured small intestinal stem cells retain the capacity for morphogenesis

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The culture of small intestinal stem cells (SISCs) with expansion of cell numbers could facilitate extensive mucosal replacement from minimal donor tissue. However, enterocytes in culture dedifferentiate and SISCs may lose their capacity for morphogenesis. This study characterized epithelial cells in culture and assessed whether culture before transplantation affects the regenerative capacity of SISCs.

Rat small intestine was disaggregated using collagenase and Dispase digestion. This releases cell aggregates containing SISCs, which were then cultured for 4 days. Cell proliferation was assessed by crystal violet assay and cell morphology by histochemistry, immunohistochemistry and electron microscopy. Cultured cells were then grafted with fetal intestinal mesenchyme to athymic mice and retrieved after 7 or 14 days for histological evaluation.

Cell numbers increased tenfold *in vitro*. Over 90 per cent of cells showed an enterocytic phenotype with expression of alkaline phosphatase, cytokeratins 8, 18 and 19, and microvillus brush borders. Cells transplanted after 4 days in culture showed progressive morphogenesis with development of a simple polarized epithelium at day 7 and rudimentary crypt and villus structures by day 14, which expressed distinct stem-cell lineages including goblet cells and enterocytes.

In conclusion, epithelial SISCs retain a multipotent capacity for epithelial regeneration after short-term primary culture and transplantation. The ability to culture SISCs should allow molecular manipulation before syngeneic stem-cell transplantation.

Modulation of impaired cellular function in intraperitoneal sepsis by pentoxifylline

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In sepsis, cell membrane dysfunction can lead to hyponatraemia with resultant morbidity and mortality. Resting membrane potential (RMP) is a measure of cellular function and reflects ion distribution across the cell membrane. Therapy that improves the RMP in sepsis may potentially be useful in electrolyte management. Pentoxifylline (oxpentifylline) may act by stabilizing the cell membrane and inhibiting tumour necrosis factor. A caecal ligation and puncture (CLP) model was used to mimic clinical sepsis.

Wistar rats (170–250 g) were randomly allocated into six groups of 24 animals. Pentoxifylline was administered intraperitoneally, 20 mg per kg body-weight, at the various time intervals. RMP was measured at 6, 12 and 18 h after operation using a microelectrode inserted into the thigh musculature.

Time after surgery (h)	Sham	CLP	Pentoxifylline given 1 h before CLP	Pentoxifylline given 1 h after CLP	Pentoxifylline given 10 h after CLP	Pentoxifylline given 16 h after CLP
6	−83·1(0·6)	−82·1(0·6)	−82·8(2·8)	−81·6(1·2)	—	—
12	−80·4(1·1)	−77·9(1·1)	−81·6(1·8)	−81·0(1·9)	−83·9(0·8)*	—
18	−82·1(0·7)	−76·2(0·7)	−77·8(1·8)	−86·8(2·2)†	−85·4(1·2)†	−83·1(0·6)*

Values are mean(s.e.m.) RMP expressed as mV. *$P<0{\cdot}01$, †$P<0{\cdot}001$ (intergroup analysis using the Newman–Keul test). Two-way analysis of variance gave $P<0{\cdot}02$ at 12 h and $P<0{\cdot}001$ at 18 h

In conclusion, administration of pentoxifylline after the establishment of sepsis reliably prevents decreases in RMP. Pentoxifylline should be investigated for its clinical value in sepsis.

Effects of octreotide, insulin, epidermal growth factor and gastrin on the proliferation of tumorigenic cells *in vitro*

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There is evidence that the growth of a number of human tumours is stimulated by peptides and growth factors such as insulin, epidermal growth factor (EGF) and gastrin. Since octreotide (somatostatin; SMS) inhibits the growth of some experimental tumours *in vivo*, its effects alone or in combination with insulin, EGF and gastrin on the proliferation (uptake of [^{3}H]thymidine) of three tumorigenic cell lines were investigated *in vitro*. The proliferation of HSN cells (fibrosarcoma) and K12-Tr and WB2054M cells (colonic adenocarcinomas) was assessed in the presence of SMS (125 μg ml^{-1}), insulin (12·5 μg ml^{-1}), EGF (1·25 ng ml^{-1}), gastrin (5 nmol l^{-1}) and saline (control) alone or with SMS in combination, in the presence of [^{3}H]thymidine for 48 h.

	Cell type		
	HSN	K12-Tr	WB2054M
SMS	−28·0	−25·6	−19·6
Insulin	29·1	16·6	28·6
SMS plus insulin	1·5	−14·7	6·0
EGF	45·7	14·0	16·4
SMS plus EGF	−14·1	2·4	−8·2
Gastrin	15·5	−5·6*	29·8
SMS plus gastrin	−12·2	−15·6	11·2

Values are percentage change in [^{3}H]thymidine uptake compared with controls. **P* not significant (analysis of variance)

These results indicate that SMS not only significantly inhibits cell proliferation *in vitro* but also reduces the stimulatory effects of insulin, EGF and gastrin. These observations suggest that the inhibitory effect of octreotide on the growth of tumour *in vivo* may be mediated, at least in part, by its antiproliferative action.

Polymorphonuclear cytokine production after thermal injury

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The polymorphonuclear leucocyte (PMN) is a fundamental participant in the inflammatory process. It has recently been shown to be capable of both synthesis and release of numerous cytokines in response to mitogenic or antigenic stimulation. PMN cytokine production in patients following thermal injury, however, has yet to be demonstrated.

Highly purified populations of PMNs were isolated from the peripheral blood of patients following thermal injury. Cells were cultured in the presence or absence of bacterial endotoxin (lipopolysaccharide; LPS) stimulation for varying periods of time and compared with PMNs from normal controls. Total RNA was isolated and messenger RNA (mRNA) expression determined by Northern blot analysis using radiolabelled complementary DNA (cDNA) probes for interleukin (IL) 1, IL-6 and tumour necrosis factor (TNF) α.

mRNAs for IL-1 and TNF were expressed only after *in vitro* stimulation with LPS and both decreased following thermal injury. mRNA for IL-6, however, was constitutively expressed by PMNs from both normals and patients. *In vitro* LPS stimulation increased the expression of mRNA for IL-6 in normal PMNs but had no demonstrable effect on the PMNs from thermally injured patients. No decrease in the expression of mRNA for IL-6 was observed following thermal injury.

It is concluded that the PMN is an important source of inflammatory cytokine production following thermal injury. The quantitative predominance of the PMN following such injury establishes its role as an important modulator of both cellular and humoral immune responses in the thermally injured patient.

Role for nitric oxide in pancreatitis-induced lung injury

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Nitric oxide (NO) is an endogenous vasodilator that also inhibits neutrophil activation and adherence to endothelial cells. Inactivation of NO by superoxide anion released from activated neutrophils, inducing neutrophil-mediated microvascular injury, may be central to adult respiratory distress syndrome. The effect of increasing NO concentration, with sodium nitroprusside (SNP), on lung injury associated with pancreatitis was evaluated.

Sprague–Dawley rats were randomized to control (saline infusion) or caerulein-induced pancreatitis groups, which were treated with saline or sodium nitroprusside (0·4 mg kg^{-1}). The myeloperoxidase (MPO) concentration was used to measure neutrophil infiltration in the lung. Wet:dry lung weights and broncheolar lavage protein (BAL protein) level were used to measure pulmonary microvascular permeability.

Caerulein (5 μg kg^{-1} h^{-1}) induced pancreatitis in all animals, with a mean(s.e.m.) increase in serum amylase concentration from 1851(208) units l^{-1} (control) to 5198(924) units l^{-1} (pancreatitis) ($P < 0{\cdot}05$).

	Control ($n = 10$)	Pancreatitis ($n = 10$)	SNP ($n = 10$)
MPO (units per g)	2·1(0·5)	7·3(0·7)†	2·5(0·4)§
Wet:dry weight	3·0(0·0)	8·6(1·9)†	3·0(0·1)§
BAL protein (mg)	347(32)	6024(209)*	1441(166)‡

Values are mean(s.e.m.). *$P < 0{\cdot}05$, $P < 0{\cdot}001$ *versus* control; ‡$P < 0{\cdot}05$, §$P < 0{\cdot}005$ *versus* pancreatitis (all Student's unpaired *t* test)

These data show that pancreatitis induced significant pulmonary neutrophil influx and microvascular leakage, which were attenuated by SNP. They support the hypothesis that inactivation of endogenous NO may in part be responsible for neutrophil-mediated lung injury in pancreatitis and suggest a possible therapeutic role for NO.

Exercise induces neutrophil activation in claudicants but not in age-matched controls

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Claudicants have a mortality rate from cardiovascular disease that is three times that in men of the same age. Recent evidence not only implicates neutrophils in the pathogenesis of atherosclerosis but also suggests that exercise in claudicants results in neutrophil activation. When activated, neutrophils may adhere to the endothelium and release elastase and oxygen-derived free radicals.

With ethical committee approval, 27 claudicants and 15 healthy controls were studied. All claudicants had ankle:brachial pressure indices (ABPIs) $\leq 0{\cdot}95$ and arterial disease proven by angiography. Controls had no history of cardiovascular disease and ABPIs $> 0{\cdot}95$. After informed consent, all subjects were rested supine for 1 h. Blood samples were then taken for measurement of free radical activity and plasma elastase concentration, before and after a period of standardized treadmill exercise. Free radicals cause the plasma thiol:albumin (PSH:Alb) ratio to fall and lipid peroxide concentration (e.g. malondialdehyde (MDA)) to rise.

	Before exercise	After exercise	*P**
Claudicants			
MDA (nmol ml^{-1})	7·8 (6·7–9·9)	8·7 (7·6–11·1)	<0·001
PSH:Alb	114 (103–120)	107 (95–118)	<0·01
Elastase (ng ml^{-1})	23 (12·9–33·6)	29 (19·1–36·2)	<0·01
Controls			
MDA (nmol ml^{-1})	6·9 (5·8–7·8)	7·3 (6·6–8·4)	n.s.
PSH:Alb	118 (100–123)	120 (107–127)	n.s.
Elastase (ng ml^{-1})	20 (16·6–25·7)	24 (21·3–29·0)	n.s.

Values are median (interquartile range). *Wilcoxon paired test; n.s., not significant

These results show that exercise causes neutrophil activation in claudicants only. Both elastase and free radicals cause endothelial damage. Exercise-induced neutrophil activation may therefore contribute to the higher cardiovascular mortality rate seen in claudicants.

Immunological alterations in patients undergoing open and laparoscopic surgery

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Abnormal release of inflammatory mediators following surgical injury is associated with immunological alteration that may predispose to sepsis. Laparoscopic surgery is associated with fewer postoperative complications, but mechanisms are unclear. It was hypothesized that the early recovery seen following laparoscopic surgery may relate to minimal impairment of immune function. This study analysed temporal immune responses in two similar groups of patients randomized to open ($n=15$) or laparoscopic ($n=15$) cholecystectomy.

Patients were matched for age, height, weight, American Society of Anesthesiologists score, anaesthetic used and operation time. The length of hospital stay and complications were recorded. Immune parameters measured included monocyte superoxide anion (O_2^-) and tumour necrosis factor (TNF) release, as well as polymorphonuclear neutrophil (PMN) chemotaxis and O_2^- release. White cell count (WCC) and arterial partial pressure of oxygen (P_{aO_2}) were assessed before operation and on day 1 after surgery.

	Open cholecystectomy	Laparoscopic cholecystectomy
Monocyte O_2^- release ($\times 10^{-2}$ nmol)	1·1(0·8)	0·1(0·2)*
TNF (pg)	217(122)	14·4(0·6)*
PMN chemotaxis	149(86)	−28(11)*
PMN O_2^- release ($\times 10^{-2}$ nmol)	18·4(5·5)	2·4(3·1)*
WCC ($\times 10^4$ ml^{-1})	10·3(5·0)	2·1(1·6)*
P_{aO_2} (kPa)	2·6(0·5)	0·7(0·3)*

Values are mean(s.d.) difference before and on day 1 after surgery. $^{*}P<0\cdot001$ *versus* open procedure (Student's *t* test)

There were significant increases in monocyte O_2^- and TNF release, as well as in PMN chemotaxis, O_2^- release and WCC in the open *versus* laparoscopic cholecystectomy groups, with a concomitant decrease in P_{aO_2}. These differences correlated with a significant increase in the length of hospital stay ($P<0\cdot05$) and respiratory complications ($P<0\cdot05$) in the open surgery group.

This study demonstrates that the beneficial effects of laparoscopic surgery are due, in part, to preservation of immune function in the postoperative period.

Cell membrane vesicle production for the derivation of antiendothelial cell antibodies

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The effectiveness of antiepithelial monoclonal antibodies (MAbs) in the imaging and treatment of tumours is limited by antigen expression and deficiencies of tumour microcirculation. The aim of this study was to isolate tumour endothelial cell membrane antigens (ECMAs) for derivation of antiendothelial cell MAbs.

Six tumour-bearing organs (placenta, two; kidney, two; lower-limb sarcoma or melanoma, two) were perfused at 120 mmHg in an *ex vivo* system (modified Krebs' solution, 95 per cent oxygen saturation, 37°C) with the chemical vesicant *n*-ethyl maleimide (150 mg dl^{-1}) for 1 h. Perfusate was differentially centrifuged (25–150 000*g*). Vesicles were dialysed against 0·1 mol l^{-1} phosphate-buffered saline and characterized with respect to phosphate content, electron microscopy and immunocytochemistry (*Ulex europeaeus* lectin type I, antithrombomodulin, β_2-microglobulin).

Renal adenocarcinoma vesicles (500 μg protein per ml) were injected intraperitoneally into BALB/c mice ($n=6$) at a dose of 50 μg per mouse. Eight MAbs were isolated by limiting dilution hybridoma techniques. RB-1 MAb demonstrated organ specificity, binding only to kidney endothelium. RB-2 demonstrated pan-human organ specificity. Six MAbs failed to demonstrate endothelial specificity.

Ex vivo endothelial cell vesicle production is an effective method of isolating ECMAs for potentially deriving antiendothelial cell MAbs.

Paradoxical rise in neutrophil L-selectin in septic shock

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Neutrophil adhesion to endothelium requires the attachment and subsequent shedding of the neutrophil adhesion molecule L-selectin. Further adhesion is mediated by the β_2-integrins, including cluster designation (CD) 11b. As intravascular neutrophil activation may be the cause of organ failure (multiple organ dysfunction syndrome (MODS)) seen in sepsis, expression of these molecules in patients with MODS and systemic inflammatory response syndrome (SIRS) (no organ failure) was compared with that in control subjects.

Nine patients (median age 74 (range 49–88) years) with MODS were compared with six (median age 72 (range 54–80) years) with SIRS and 14 controls (median age 44 (range 21–81) years).

Neutrophils were labelled with fluorescein-conjugated monoclonal antibodies and median fluorescence measured by flow cytometry.

	Control	SIRS	MODS
L-selectin	6·5 (5·1–13·1)	9·8 (3·1–15·4)	21·1 (7·2–41·6)*
CD11b	22·2 (11·3–75·6)	22·1 (14·4–52·7)	65·6 (26·9–80·4)*

Values are median (range). $^{*}P<0\cdot05$ *versus* control

Thus, in MODS, failure of L-selectin to shed is paradoxically associated with the upregulation of CD11b. These changes may be crucial in the development of MODS as they may allow the activated neutrophil to 'roll' on the endothelium, resulting in diffuse damage.

Chemokine Rantes and traffic of lymphocytes in acute inflammation

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The inflamed human appendix has been demonstrated to recruit 'memory' T lymphocytes (CD3$^+$, CD45R0$^+$) selectively from the peripheral circulation. It was used as a model of acute inflammation in this study. The chemotactic cytokine Rantes is known to cause selective chemotaxis of 'memory' T lymphocytes *in vitro*. The appendices of 25 patients (15 acutely inflamed, ten histologically normal) were studied in an attempt to establish the role of Rantes in the recruitment of 'memory' T lymphocytes *in vivo*.

Immunocytochemical investigation of inflamed appendices using a monoclonal antibody demonstrated increased expression of Rantes compared with minimal staining in histologically normal appendices. Flow cytometric analysis of appendiceal lymphocytes showed significantly increased levels of Rantes expression when the organ was inflamed.

	Positive appendiceal cells (%)		
Histology	Rantes$^+$	Rantes$^+$/CD3$^+$	Rantes$^+$/CD45R0$^+$
Normal	0·6	0·3	0·5
Acute	7·5*	5·0*	7·5*

Values are means. $^{*}P<0\cdot01$

Rantes positivity was predominantly in the 'memory' T lymphocyte population. *In situ* hybridization using a digoxigenin-labelled messenger RNA (mRNA) probe confirmed the upregulation of mRNA for Rantes in inflamed appendices compared with its near absence in the normal group.

It is concluded that Rantes secretion is a significant component in the active recruitment of 'memory' T lymphocytes to the inflamed human appendix. This mechanism may be a general feature of T lymphocyte recruitment *in vivo*.

Defect in phagocytosis induced by blood transfusion

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Blood transfusion is an independent risk factor for infection following elective and emergency surgery. The mechanism for this is unknown but no studies exist of the effects of transfusion on the opsonic capacity of serum or on the phagocytic ability of neutrophils. Measurement was made of the phagocytosis of fluorescein-labelled *Staphylococcus aureus*, whose injestion by neutrophils is quantified by flow cytometry.

Staphylococcal phagocytosis was measured in ten patients before and 24 h after homologous blood transfusion (2–4 units), the bacteria being opsonized with a control serum. In addition, the opsonizing capacity of serum taken from patients before and after transfusion was quantified by the same technique using neutrophils from healthy donors.

	Before transfusion	After transfusion	*P*
Patient neutrophils			
Control serum	246·2(18·1)	694·5(249·2)	<0·01
Patient serum	299·8(29·2)	310·1(27·5)	n.s.
Control neutrophils			
Control serum	524·7(55·0)	—	—
Patient serum	477·0(64·9)	394·4(29·3)	<0·05

Values are mean(s.e.m.) mean channel fluorescence. n.s., Not significant

Thus, after transfusion, neutrophils have an increased capacity to ingest optimally opsonized bacteria. However, post-transfusion serum is less capable of opsonizing bacteria for ingestion than pretransfusion and healthy serum. Transfusion causes an increase in neutrophil phagocytosis but at the same time an opsonic defect. These findings may help to elucidate the increased susceptibility of patients to infection after blood transfusion.

Flow cytometric analysis of *in vivo* 5-bromo-2′-deoxyuridine labelling of gastric cancer: a valid interinstitutional technique for measuring proliferative indices

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Multiparameter flow cytometric analysis of gastric carcinoma labelled *in vivo* with 5-bromo-2′-deoxyuridine (BrdU) allows measurement of proliferative indices, including total (TLI) and aneuploid (AnLI) labelling indices, S phase duration (T_s), potential tumour doubling time (T_{pot}) and tumour heterogeneity. It has been suggested that such data may have prognostic and therapeutic application. However, considerable interinstitutional variation may exist with complex analyses, being in part observer-dependent.

The aim of this study was to measure the proliferative indices of 53 gastric tumours and compare the data from independent analyses in each institution. Tumours were labelled with 200–250 mg BrdU 2·5–15·75 h before surgery over a 4-year period from 1988 to 1992. Statistical analysis was performed using the Mann–Whitney *U* test and the Bland–Altman test.

	Institution 1			Institution 2		
Proliferative index	Aneuploid ($n=17$)	Diploid ($n=36$)	*P*	Aneuploid ($n=22$)	Diploid ($n=31$)	*P*
TLI	2 (0·4–12·9)	7 (1·9–21)	<0·0001	3·7 (1–10·8)	6·5 (1·4–18)	0·002
AnLI	8·6 (4·3–21)	—	—	10 (1·4–20)	—	—
T_s	9·4 (1·3–39)	12 (1·8–49)	0·36	9 (5–32)	11·4 (6·2–25)	0·17
T_{pot}	23 (3·3–80·5)	4·5 (0·5–27)	<0·0001	11·5 (2·6–32)	4 (1·4–31)	<0·0001

Values are median (range)

There were statistically significant differences in TLI and T_{pot} between aneuploid and diploid tumours. BrdU is a robust marker from which proliferative data are routinely obtained by flow cytometric analysis. There was no significant difference between population measurements for each of the proliferation indices in either institution, except for T_{pot}. However, there were significant differences for individual tumours identified by the Bland–Altman test. Further standardization of analytical techniques will improve the application of proliferative assays in solid tumours.

Proliferating cell nuclear antigen and p53: failed markers of outcome in gastric cancer

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It has been suggested that new markers of tumour biology will help to determine prognosis in patients with solid tumours. In particular, proliferating cell nuclear antigen (PCNA) and mutations of the oncosuppressor gene p53 have been reported as markers of poor prognosis in gastric cancer.

Immunohistochemical investigation was carried out on 76 formalin-fixed gastric cancers using the monoclonal antibody PC10 against PCNA and the polyclonal antibody CM1 to the p53 protein product. The results of PCNA and p53 staining were compared with tumour node metastasis (TNM) status, tumour stage and patient survival. Most tumours showed heterogeneity of staining. PCNA expression did not correlate with TNM status, stage ($P>0·1$) or survival ($P=0·57$). The incidence of p53-negative tumours was higher in the group with metastatic disease. Patients in the p53-positive group had a 30 per cent 5-year survival rate compared with 15 per cent in the p53-negative group.

Neither PCNA nor p53 protein product expression was shown to have any adverse prognostic influence in this series. The variability of expression suggests that these markers are unlikely to be robust predictors of outcome in patients with gastric cancer.

Exfoliative brush cytology as an adjunct to endoscopic biopsy in the detection of upper gastrointestinal malignancy

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The role of exfoliative cytology as an adjunct to endoscopic biopsy in the detection of upper gastrointestinal malignancy is controversial in so far as some claim that its use is of little clinical benefit. The role of cytology in the differentiation of benign from malignant mucosal lesions in 2183 consecutive patients who underwent oesophagogastroduodenoscopy was examined.

Malignancy was confirmed in 394 patients. Both endoscopic biopsy and cytology were positive in 275 (69·8 per cent). Endoscopic biopsy suggested the diagnosis in the presence of negative cytology in 73 (18·5 per cent) of 394 patients, while cytology was positive after a negative biopsy in 36 (9·1 per cent) of 394. Ten (2·5 per cent) of 394 patients were not diagnosed before operation using either method.

Endoscopic biopsy yielded a sensitivity of 88·3 per cent, a specificity of 99·9 per cent, a positive predictive value of 99·7 per cent and a negative predictive value of 97·6 per cent. Cytology alone, on the other hand, yielded a sensitivity of 79·0 per cent, a specificity of 98·5 per cent, a positive predictive value of 92·0 per cent and a negative predictive value of 95·7 per cent. With the additional use of cytology, the diagnostic yield was increased from 88·3 to 97·5 per cent.

It is concluded that upper gastrointestinal exfoliative cytology is a useful adjunct in the investigation of patients with suspicious mucosal lesions.

Effect of chemoradiotherapy on oesophageal motility

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Dysphagia in oesophageal carcinoma may reflect luminal obstruction or motility disturbance. The effect of chemoradiotherapy (CR) on motility is unknown. Stationary manometry and 24 h pHmetry was performed in eight patients with oesophageal carcinoma before and 2 weeks after the completion of a CR regimen of 5-fluorouracil, cisplatin and 40-Gy radiotherapy. Oesophageal body pressure waves were categorized as propagated, simultaneous, non-transmitted or isolated.

	Before operation	After operation	*P*†
Propagated waves (%)*	28·8(11·5)	52·2(11·9)	0·03
Simultaneous waves (%)*	28·6(12·6)	18·8(11·3)	0·26
Non-transmitted waves (%)*	23·3(13·7)	3·3(2·3)	0·13
Isolated waves (%)*	7·8(5·7)	14·4(7·8)	0·25
No. with acid reflux	4	3	n.s.

*Values are mean(s.e.m.). †Wilcoxon signed rank test; n.s., not significant

All patients with oesophageal carcinoma had abnormal motility. The propagation of waves increased significantly following CR, corresponding with a reduction (but not elimination) of the tumour mass in all patients. There was a trend towards normality in isolated, simultaneous and non-propagated waves. It is concluded that oesophageal dysmotility due to tumour is partially reversed by CR.

Haemorrhagic shock and lower oesophageal sphincter pressure: an experimental model

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Aspiration is a frequent problem in shocked patients but the role of the physiological barrier, the lower oesophageal sphincter (LOS), has received little attention. The effect of hypotension, induced by haemorrhage, on LOS pressure (LOSP) was examined in seven adult mongrel dogs acting as their own controls. Animals were studied under general anaesthesia induced by thiopentone and maintained with 0·5–1·0 per cent enflurane. Blood pressure (BP) was reduced in two phases: mean BP reduced to 80 per cent (BP1) and then to 60 per cent (BP2) of control value and maintained at each of these values for 15 min. BP was monitored by intra-arterial catheter and heart rate by electrocardiographic tracing. BP was then restored to prehaemorrhage levels via autologous retransfusion. LOSP was recorded continuously using a solid-state sleeve catheter.

	Heart rate (beats per min)	Mean BP (mmHg)	Mean(s.e.m.) LOSP (mmHg)
Control	88	88	13·4(1·7)
BP1 (20% reduction)	107*	70	12·0(0·8)
BP2 (42% reduction)	101	51	7·7(0·8)†
Retransfused	100	92	13·6(1·3)

$^*P < 0·05$, $^†P < 0·01$ *versus* control (Wilcoxon signed rank test)

Haemorrhage producing a 42 per cent drop in the mean BP led to a significant fall in LOSP. This was restored to normal following autologous retransfusion. This may explain the high incidence of aspiration pneumonia in hypotensive patients and provides a useful model for prophylactic manipulation of LOSP.

Hypochlorhydria as a factor in the aetiology of gastroparesis in functional dyspepsia

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Disordered gastric motor function is common in functional dyspepsia (FD) but the causative mechanism is poorly understood. In this study 83 patients were diagnosed as having functional FD after exclusion of peptic ulcer, gallstones, gastro-oesophageal reflux and irritable bowel syndrome. Patients were investigated by scintigraphic solid-meal gastric emptying (GE), peak acid output (PAO) following pentagastrin stimulation, and gastric biopsies. GE was validated in 15 controls.

Overall GE was delayed in FD compared with controls (mean t_{50} 100 (95 per cent confidence interval (c.i.) 90–111) *versus* 67 (57–78) min; $P < 0·001$, Mann–Whitney U test). This delay was due to a decrease in the mean emptying rate (ER) (0·019 (95 per cent c.i. 0·016–0·021) in FD *versus* 0·026 (0·020–0·032) min^{-1} in controls; $P < 0·01$, Mann–Whitney U test). Lag phase duration in FD did not differ from that in controls (mean t_{lag} 30 (95 per cent c.i. 23–36) *versus* 21 (14–27) min; $P = 0·09$, Mann–Whitney U test). Overall PAO was within the normal range (mean 25 (95 per cent c.i. 20–30) mmol h^{-1} in men and 21 (16–25) mmol h^{-1} in women), but 13 patients had hypochlorhydria. Gastritis was present in 34 patients and *Helicobacter pylori* in 31.

Helicobacter colonization was related to severity of gastritis ($r = 0·73$, $P < 0·01$, Pearson's product moment test of correlation). Severe gastritis was associated with decreased acid secretion. In all patients, delay in GE was associated with decreased PAO ($r = -0·33$, $P < 0·01$, Pearson's product moment test of correlation). A marked delay in GE was evident in the 13 patients with hypochlorhydria (mean t_{50} 143 (95 per cent c.i. 101–186) min).

Hypochlorhydria may be an end-stage phenomenon of *Helicobacter* gastritis and the loss of acid–peptic activity impairs GE causing gastroparesis, a dominant abnormality in functional dyspepsia.

Ambulatory 24-h bile reflux monitoring in Barrett's oesophagus

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Reflux of bile has been implicated in Barrett's oesophagus, but assessment of this problem has been impractical, requiring aspiration studies that are both cumbersome and non-physiological. Bilitec 2000 allows 24-h ambulatory monitoring of gastric or oesophageal bile using an optical fibre sensor and the spectrophotometric properties of bilirubin (peak 453 nm).

Simultaneous 24-h ambulatory monitoring of oesophageal bile and dual-channel (gastric and oesophageal) pH studies were carried out in two groups of patients. Group 1 ($n = 5$) were normal controls; group 2 ($n = 7$) were patients with Barrett's oesophagus.

	Controls ($n = 5$)	Barrett's oesophagus ($n = 7$)
Bile absorbance (percentage of time >0·15 supine)	1·6(0·9)	20·8(4·3)*
DeMeester acid score	6·6(2·2)	68·2(18·8)*
Percentage of time oesophageal pH > 7·5	4·5(4·4)	0·4(0·3)
Percentage of time gastric pH > 4 (supine)	3·1(1·9)	5·3(4·2)

Values are mean(s.d.). $^*P < 0·01$ (Wilcoxon rank sum test)

The ambulatory bile reflux monitor detected significant concentrations of bile in the oesophagus of patients with Barrett's oesophagus compared with controls. There was no increase in oesophageal pH and no significant gastric alkaline shift, indicating that bile reflux may occur in the presence of a low pH.

It is concluded that the bile probe provides a useful and practical assessment of oesophageal bile reflux problems.

Quantification and localization of epidermal growth factor receptor in gastric cancer

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Overexpression of epidermal growth factor receptor (EGFR) may be related to poor prognosis and advanced stage in gastric cancer. Quantification of receptors using established radioligand binding assays on membrane preparations may be inaccurate due to variable stromal contamination and provides no information on cellular localization. Immunohistochemical techniques produce only semiquantitative results. The aim of this study was to quantify and localize EGFR expression in tumours to increase the understanding of receptor biology.

Forty frozen gastric tumours and mucosal controls were examined. A quantitative autoradiographic technique using a ^{121}I-labelled monoclonal antibody EGFR-1 was compared with a standard three-layer immunohistochemical technique for assessing EGFR expression in 5-μm sections. An automated Joyce–Lobel image analysis system was used for counting labelled receptors in ten (×40) high-powered fields per section and reproducibility confirmed on duplicate samples.

	Autoradiography (receptors per cell)	Immunohistochemistry (grade)
Gastric tumours		
$n = 8$	$4–10 \times 10^3$	–
$n = 22$	$2·3–9·9 \times 10^4$	+
$n = 6$	$1·2–5·9 \times 10^5$	+ +
$n = 4$	$1·2–1·7 \times 10^6$	+ + +
Controls		
Mucosa ($n = 40$)	$1–4 \times 10^4$	+
Normal skin (dermis)*	2×10^5	+ +
A431 cells*	2×10^6	+ + +

*Internal calibration control

With this novel technique, EGFR-negative tumours were found on immunohistochemical staining to have fewer receptors per cell than normal mucosa. Receptor internalization or a decrease in EGFR messenger RNA could account for this finding. This technique could also be used for other antigenic markers and for identifying heterogeneity in tumours.

Organotypical mucosal morphogenesis occurs during regeneration, in the absence of luminal contents

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After mucosal injury, stem cells restore normal epithelium by organotypical morphogenesis, while abnormal regeneration may result in metaplasia. The relative roles of regulatory factors on this process remain obscure and include (1) stem-cell 'niche' factors and (2) luminal content. To investigate these factors, disaggregated epithelium was grafted to an ectopic subcutaneous site and the capacity for organotypical mucosal regeneration assessed in the absence of luminal content.

Cell aggregates containing small intestinal stem cells were isolated from postnatal inbred rats by enzymatic digestion and then grafted to adult recipients. Fifty subcutaneous transplantations were performed. The transplants were retrieved after 14 days; morphology was assessed by histology and cell proliferation by autoradiography. Stem-cell lineage studies used alkaline phosphatase to identify enterocytes and alcian blue for goblet cells; polyclonal antibodies against lysozyme and serotonin were used to identify Paneth and enteroendocrine cells.

Some 80 per cent of subcutaneous transplants regenerated neointestinal structures, with well formed crypts and villi. Proliferation was confined to basal crypt regions, as occurs in normal intestine. All stem-cell progeny were identified within this neomucosa.

In conclusion, stem cells regenerate organotypical small intestinal neomucosa after transplantation to ectopic sites. Thus, stem-cell niche factors (epithelial–mesenchymal interactions) are more important than luminal content in directing mucosal regeneration.

Relationship between tumour size and quality of life in patients with colorectal liver metastases

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The justification for palliative chemotherapy is that control of tumour size improves physical and mental well-being. However, chemotherapy has side-effects and tumour size may not be the crucial influence on mental and physical well-being in patients with cancer. The relationship between mental and physical symptoms and tumour size was assessed in patients with colorectal liver metastases.

Ninety-five patients with colorectal metastases confined to the liver underwent regular computed tomography and completed quality-of-life questionnaires to assess physical (Rotterdam Symptom Checklist, Sickness Impact Profile (SIP)) and mental (Hospital Anxiety and Depression scale, SIP) status.

There was a significant ($P < 0{\cdot}01$) correlation between the extent of liver disease and physical symptoms ($r = 0{\cdot}6$), anxiety ($r = 0{\cdot}3$) and depression ($r = 0{\cdot}5$). Patients treated by intrahepatic artery chemotherapy subsequently had tumour shrinkage, which did not occur in the no-treatment controls. This was associated with a significant improvement ($P < 0{\cdot}05$, Mann–Whitney U test) in physical symptoms, anxiety and depression.

It is concluded that control of tumour size with palliative chemotherapy improves physical and mental well-being.

New prognostic variable for rectal cancer

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A sizeable minority of rectal carcinomas show a cribriform growth pattern (microacinar) rather than large irregular tubules. This study aimed to evaluate the prognostic value of this histological variable.

A total of 138 consecutive patients undergoing radical rectal excision who had a complete 5-year follow-up or known recurrence were staged by the schemes of Dukes and Jass. The median follow-up for survivors was 95 (range 11–204) months and 35·5 (range 3–120) months for those who died. Tumour acini were classified according to their size into microacinar (28) and macroacinar (108). Patients with microacinar structures had a significantly worse 5-year survival rate than those with macroacinar (43 *versus* 68 per cent; $P = 0{\cdot}01$, log rank analysis) and a higher 5-year recurrence rate (64 *versus* 42 per cent; $P = 0{\cdot}04$, log rank analysis). The size of the acinar structure had independent prognostic value for survival (relative risk 2·60, $P = 0{\cdot}003$, Cox regression analysis). This was true even when Dukes' or Jass' classification was included in the model (relative risk 2·18, $P = 0{\cdot}02$ and 2·46, $P = 0{\cdot}004$ respectively).

These data show that classifying rectal cancer as microacinar or macroacinar adds prognostic value to Dukes' and Jass' classifications. This may be a more objective criterion than conventional histological grade.

Prolonged administration of levamisole in the adjuvant setting

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It has been suggested that the apparent synergistic effect of 5-fluorouracil (5-FU) and levamisole is due to the immunomodulatory effects of levamisole. To investigate this, natural killer (NK) cell cytotoxicity was assessed before operation, in the immediate postoperative period and 3 months after operation in 20 patients with Dukes' B_2 or C tumours randomized to receive: (1) surgery alone ($n = 7$); (2) surgery with 5-FU 450 mg m^{-2} plus levamisole 150 mg ($n = 7$); (3) surgery with 5-FU plus folinic acid 20 mg m^{-2} ($n = 6$).

Induction of chemotherapy was for 3 days, starting the day after operation; chemotherapy was continued weekly for 6 months. NK cell cytotoxicity was measured by a standard chromium release assay against a K562 cell target and results expressed as the percentage lysis achieved at an effector:target ratio of 20:1.

	Before operation	Day 5 (after induction of chemotherapy)	At 3 months (during weekly maintenance)
Surgery alone	34·0 (17·0–40·6)	17·0 (9·8–33·6)	28·0 (20·6–32·6)
5-FU plus levamisole	30·0 (25·5–31·0)	37·5 (23·9–46·0)*	33·1 (22·5–39·1)
5-FU plus folinic acid	39·0 (29·5–49·5)	19·4 (10·5–21·2)*	30·8 (23·0–39·0)

Values are median (interquartile range). *$P < 0{\cdot}05$ (Mann–Whitney U test)

Levamisole, when given with 5-FU, led to a quicker recovery of immune function in the immediate postoperative period, but did not influence immune function during maintenance chemotherapy. These findings question the need for prolonged administration of levamisole in the adjuvant setting.

Intraoperative lavage with short-chain fatty acids and glucose promotes anastomotic healing in the colon

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The type of fluid used during intraoperative lavage may influence the healing of a left-sided colonic anastomosis performed for obstruction. This possibility was investigated in 120 Wistar rats.

Primary colonic anastomosis was performed in five groups of rats 24 h after ligature obstruction of the rectosigmoid. Rats were lavaged with saline, 10 per cent glucose, 10 per cent povidone–iodine, a short-chain fatty acid (SCFA) solution or had no lavage (controls). Maximum bowel wall tension during resistance to hydrostatic pressure and hydroxyproline content were measured 3 and 6 days after surgery.

Mean(s.d.) bowel wall tension was raised over control values at 3 days in rats lavaged with glucose (29(10) *versus* 12(12) $\times 10^3$ dynes cm^{-1}; $P < 0{\cdot}01$) and SCFAs (30(8) $\times 10^3$ dynes cm^{-1}; $P < 0{\cdot}05$) and over controls at 6 days in those lavaged with povidone (77(8) *versus* 58(19) $\times 10^3$ dynes cm^{-1}; $P < 0{\cdot}05$) and glucose (85(13) $\times 10^3$ dynes cm^{-1}; $P < 0{\cdot}01$). In all groups at 3 days hydroxyproline content fell at the anastomosis compared with the value in the proximal and distal colon ($P < 0{\cdot}05$–$0{\cdot}001$). Thereafter, the content rose in all lavaged groups, reaching peak values at 6 days in those receiving SCFAs (12·5(1·8) *versus* 9·1(1·6) μg mg^{-1}) in controls and 9·6(1·8) μg mg^{-1} in those receiving saline; $P < 0{\cdot}05$).

Intraoperative lavage with nutrient solutions, both SCFAs and glucose, improves colonic healing in rats.

Prospective clinical trial to determine the influence of sulindac on the formation of recurrent colonic adenomatous polyps

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Patients who develop adenomatous polyps are advised to undergo regular colonoscopy because of the risk of developing metachronous polyps, imposing strains on endoscopic resources and patients themselves.

Previous reports have suggested that sulindac is associated with regression of polyps in patients with familial adenomatous polyposis (FAP).

A double-blind randomized controlled trial was undertaken to determine whether sulindac had any influence on the rate of recurrence of polyps in non-FAP patients. A total of 100 patients who had undergone removal of colorectal carcinoma or polyps were randomized to receive sulindac 200 mg twice daily or placebo. Following colonoscopy to exclude the presence of cancer or polyps, endoscopy was performed at 6-monthly intervals. Metachronous development of a carcinoma or colonic polyp was taken as a positive endpoint.

Forty-nine patients were randomized to receive placebo and 51 to sulindac. Seven patients taking placebo and six taking sulindac developed polyps. The mean length of follow-up was 12·8 months.

No significant difference in the number of patients developing a metachronous polyp or carcinoma was detected between those receiving sulindac and those given placebo (χ^2 test). These data suggest that sulindac does not influence the rate of recurrence of adenomatous polyps.

Bilateral unstimulated gracilis neosphincter reconstruction: initial experience

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Single-muscle graciloplasty has been used for the treatment of idiopathic faecal incontinence with disappointing results. Bilateral gracilis reconstruction of the anal sphincters was used to evaluate the efficacy of using both muscles to create a more balanced sphincter complex.

Five patients, aged 18–72 years, had bilateral gracilis reconstruction (three for idiopathic faecal incontinence, one reconstruction after panproctocolectomy, one after traumatic sphincter loss) of sphincters. The mean resting and squeeze pressures before operation were 20 and 40 cmH_2O respectively. After operation the mean pressures were 50 cmH_2O (resting) and 100 cmH_2O (squeeze). All five subjects were able to hold simulated stool during defaecography. On saline continence testing, four patients were able to hold 900 ml saline without leakage but one could hold only 100 ml. Clinically, all patients were continent to liquid and solid stool. None of the patients complained of urgency or soiling after a mean follow-up of 9 months.

These initial results of bilateral gracilis neosphincter reconstruction indicate an acceptable alternative to the more expensive and difficult single-muscle stimulated graciloplasty for faecal incontinence.

$\alpha_2\beta_1$-integrin regulates the morphological differentiation of colorectal tumour cells *in vivo* and *in vitro*

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Intercellular and cell–matrix interactions are mediated through cell adhesion molecules (CAMs), of which integrins and cadherins comprise the main subgroups expressed by epithelial cells. Integrins are heterodimers composed of α and β subunits.

The expression and function of the β_1-integrin subfamily was studied in SW1222 colonic carcinoma cells. The methods used were enzyme-linked immunosorbent assay, immunohistochemistry and immunoprecipitation. Several β_1 receptors were expressed but only monoclonal antibodies to α_2 and β_1 subunits inhibited function in terms of adhesion to type I collagen (90 and 80 per cent respectively) and glandular differentiation in collagen gel (61 and 68 per cent).

This work was expanded to consider changes in the expression of integrin and other CAMs *in vivo*. Twenty-eight colorectal carcinomas and normal colonic mucosa were immunostained utilizing antibodies against β_1, α_2, α_6, α_v, $\alpha_v\beta_3$, epithelial-specific cadherin and carcinoembryonic antigen. Significant downregulation of α_2 ($P < 0{\cdot}01$) and β_1 ($P < 0{\cdot}05$) was observed in moderate and poorly differentiated tumours. Other integrins demonstrated no such loss. No correlation with Dukes' stage was found.

Loss of $\alpha_2\beta_1$ from carcinomas *in vivo*, and the observation that this is the key integrin modulating differentiation *in vitro*, are strong evidence for the role of this receptor in the biological behaviour of colorectal tumours.

Cholinergic agents modulate transport in the isolated perfused rabbit ileum

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Catecholamines, acting via the α_2-adrenergic receptor, directly influence transport in the isolated perfused ileum. This study tested the hypothesis that cholinergic agents modulate ileal transport independently of intestinal vascular resistance.

Thirty-two 10-cm segments of rabbit ileum were vascularly perfused *ex vivo* with a buffer solution containing red cells. The lumen was perfused with a buffer containing [^{14}C]polyethylene glycol. Net fluxes of water and ions (Na^+, Cl^-) were calculated during three 20-min periods: basal, drug infusion and recovery. Perfusion pressure documented changes in vascular resistance. Agents infused arterially at 10^{-5} mol l^{-1} included acetylcholine (ACh), atropine (Atr) and hexamethonium chloride (Hex). Water flux (F) and perfusion pressure (PP) are expressed as the change from basal value during drug infusion.

ACh caused significant secretion of water and ions. The infusion of Atr or Hex alone had no effect. Atr, but not Hex, prevented the prosecretory effect of ACh. There were no significant changes in perfusion pressure for any agent.

Infusion	*n*	ΔF H_2O (μl min^{-1})	ΔPP (cmH_2O)
Control	6	−2·8(8·1)	+8·2(1·1)
ACh	6	−20·2(6·2)*†	+7·5(2·7)
ACh plus Atr	4	+4·0(14·9)	+5·4(0·8)
ACh plus Hex	4	−16·7(20·2)*	+2·5(1·0)
Atr	6	−11·2(15·2)	+6·2(1·1)
Hex	6	+1·9(3·3)	+5·6(1·7)

Values are mean(s.e.m.). +, Increased absorption; −, increased secretion. *$P < 0{\cdot}05$ *versus* basal value (analysis of variance); †$P = 0{\cdot}03$ (ACh *versus* ACh plus Atr)

In conclusion, ACh causes secretion independently of changes in vascular resistance, supporting a direct effect on intestinal transport. ACh-induced secretion is mediated via Atr-sensitive muscarinic cholinergic receptors and is independent of extraintestinal neural pathways.

Reverse transcription polymerase chain reaction: a new technique for the investigation of wound repair

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A technique to detect transcripts encoding structural proteins and regulatory peptides in small wound biopsies has been developed. Regulation of the increase in the expression of types I and III procollagen is of central importance in human wound healing. The two interleukin (IL) 1 isoforms (IL-1α, IL-1β) have been identified as candidate regulatory peptides involved in this process.

With ethical committee approval, 6-mm punch biopsies were obtained weekly from ten patients with acute pilonidal sinus excision wounds. Total RNA was isolated from these biopsies. Complementary DNAs (cDNAs) were generated from the messenger RNA by reverse transcription. Polymerase chain reaction amplification of α1(I) and α1(III) procollagen and IL-1α and IL-1β cDNAs was performed using specific oligonucleotide primers.

The results show that the α1(I) and α1(III) procollagen genes are transcribed from day 3 after surgery until closure of the wound. Transcription of IL-1β was demonstrated throughout the healing process, while IL-1α transcripts were detectable only after 40 days, consistent with the results of previous *in vitro* studies.

Reverse transcription polymerase chain reaction provides a sensitive and rapid analysis of gene expression in small wound biopsies, facilitating the elucidation of biological processes in human wound healing. Its use may be further developed for diagnostic studies on small biopsies, e.g. fine-needle aspirates.

Metabolic adaptation of terminal ileal mucosa after ileoanal pouch construction

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Glutamine is the major fuel substrate for the small bowel enterocyte and butyrate that for the large bowel colonocyte. It is not known whether the terminal ileal mucosa adapts metabolically after ileoanal pouch construction.

Mucosal oxidation of three fuel substrates was assayed in triplicate biopsies from the terminal ileum or mature pouch (> 6 months since ileostomy closure) of patients with ulcerative colitis. The biopsies were incubated with either [^{14}C]glucose, glutamine or butyrate and the evolved [^{14}C]carbon dioxide captured and quantified by liquid scintillation counting. Lowry protein estimations of the biopsies were performed.

	Ileum	Pouch	*U*
Glucose ($n=8, 15$)	12·5 (3·6–22)	15 (6·0–21)	58*
Glutamine ($n=9, 14$)	77 (34–207)	24 (11–58)	28†
Butyrate ($n=9, 16$)	194 (81–321)	169 (74–726)	65*

Values are median (95 per cent confidence interval), expressed as pmol per μg mucosal protein per h. *$P>0{\cdot}05$, †$P<0{\cdot}05$ (Mann–Whitney *U* test)

In keeping with published data, butyrate was the preferred fuel substrate, followed by glutamine then glucose ($P<0{\cdot}05$). Following ileoanal pouch construction, mucosal glutamine oxidation was significantly decreased, reflecting metabolic adaptation, possibly as a consequence of faecal stasis and bacterial colonization. There was no compensatory increase in butyrate oxidation despite its production by colonizing bacteria.

Peritonitis impairs intestinal absorption of amino acids

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Sepsis adversely affects mesenteric blood flow, intestinal fine structure and mucosal barrier function. This study investigated the effect of sepsis on *in vivo* absorptive function using an experimental model of peritonitis.

Rats underwent caecal ligation and double puncture (CLP) or sham laparotomy. Animals were resuscitated with 10 ml 1 mol l^{-1} saline per 100 g body-weight subcutaneously. At relaparotomy 24 h later, the small intestine was ligated at the ligament of Treitz and the ileocaecal junction. Using a jejunal catheter, 3 ml complete defined diet and 2 ml test amino acid (2·5 μCi in 100 mmol l^{-1} cold leucine or proline) were then administered into the small intestine. Portal venous (PV) and femoral arterial (FA) sampling was performed 60 min later and the ligated gut excised for measurement of the percentage of gut residual (GR) leucine or proline in a scintillation counter.

All CLP rats had positive blood and peritoneal cultures.

			Amino acid concentration (c.p.m. per 100 μl)	
	n	GR (%)	PV	FA
Leucine				
CLP	6	67·2(3·6)*	246·6(52·6)*	223·1(55·3)*
Sham	6	18·0(3·5)	807·0(58·4)	726·4(55·4)
Proline				
CLP	6	64·7(6·0)*	369·3(81·2)*	331·5(73·5)*
Sham	6	15·1(3·7)	676·3(34·7)	615·8(15·3)

Values are mean(s.e.m.). *$P<0{\cdot}005$ *versus* sham (Student's *t* test)

GR values showed significant negative correlations with both portal and systemic concentrations of leucine and of proline ($P<0{\cdot}001$). Sepsis was therefore seen to reduce intestinal disappearance and portal and systemic appearance of luminal amino acid. This reduction in the absorptive capacity of the gut may limit the ability of enteral feeding alone to maintain nutrition during sepsis and contribute to the associated morbidity.

Selenium deficiency during total parenteral nutrition

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Selenium deficiency is increasingly recognized as a cause of disease (especially cardiac disease). Correct levels of supplementation during intravenous nutrition are unknown and high-dose replacement is potentially dangerous.

Thirty-seven patients undergoing total parenteral nutrition (TPN) were noted to be selenium deficient, 36 (5·2 per cent) of them over a 4-year period during which 690 patients were treated. Eighteen patients (49 per cent) had Crohn's disease, six (16 per cent) were neonates and 13 (35 per cent) had other diseases.

All patients receiving TPN for more than 1 month were given selenium supplementation; the initial assay of micronutrients was carried out within the first month. The time interval from starting treatment to the detection of selenium deficiency is shown.

Group	Mean time (weeks)
Crohn's disease	4·7*
Non-Crohn's	6·8*
Paediatric	6·0*

*$P>0{\cdot}05$

Three of the patients in the group with Crohn's disease developed significant complications directly attributable to selenium deficiency (one death from cardiomyopathy, one severe dysrhythmia secondary to cardiomyopathy, one difficulty in weaning from ventilatory support). Additionally, one child developed clinically increased muscular strength after selenium levels returned to normal.

Selenium deficiency may pre-exist or develop within a very short time of commencing TPN, particularly if the patient was previously malnourished. Identification of 'at risk' groups is difficult.

Hypermanganesaemia following standard total parenteral nutrition

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Hypomanganesaemia is a recorded hazard of prolonged total parenteral nutrition (TPN). Addition of this trace element to parenteral nutrition is therefore currently recommended. The normal whole blood reference range is 73–210 nmol l^{-1}. Chronic manganese poisoning has been reported at 360 nmol l^{-1}, with psychosis and parkinsonism at levels of 1000 nmol l^{-1}.

At present, the recommended daily intravenous dose of manganese for adults weighing 70 kg is 3–15 μmol.

Whole blood manganese level was monitored in 34 patients receiving standard TPN (14 g nitrogen, 11×10^3 kJ). Supraoptimal levels were found in 12 patients, four of whom had received Addamel (40 μmol manganese) daily and eight Additrace (5 μmol manganese). The mean value was 323 (range 213–928) μmol l^{-1}.

Raised levels were found to be prolonged in inpatients for several weeks after either a reduction in dosage or complete withdrawal of manganese. Initial estimates indicated a half-life of approximately 3 months.

Subsequently, all patients receiving parenteral nutrition were treated with Additrace three times per week instead of daily. However, even with this reduced level of administration, excessive levels of manganese are still being recorded.

The lack of published information about hypermanganesaemia suggests that the toxic effects are not widely understood. Monitoring of serum levels, with appropriate reduction of dosage as necessary, is therefore recommended.

Effects of lipid emulsions containing medium-chain triglycerides on phosphatidyl–inositol–glycan-linked leucocyte receptors

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It has been suggested that emulsions containing medium- and long-chain triglycerides (MCT–LCT) are a more appropriate energy source in the injured or septic patient than emulsions of LCTs alone. No comparisons exist of the effect of these two lipids on leucocyte function.

Three different classes for receptor of immunoglobulin F_c (CD16, CD32 and CD64) are differentially expressed on neutrophils and monocytes. The receptor for lipopolysaccharide (LPS)-binding protein (CD14) is expressed on monocytes only. Using fluorescent conjugated monoclonal antibodies, the expression of these receptors was examined by flow cytometry after 4 h incubation *in vitro* with either LCTs or MCT–LCT (0·5 $\mathrm{mg\,ml^{-1}}$) in a non-opsonizing medium. The data are expressed as mean(s.e.m.) of the mean channel fluorescence for each measurement ($n = 12$). Measurement was also made of the phagocytic uptake of opsonized *Staphylococcus aureus*, expressed as the phagocytic index (PI), and of LPS-stimulated production of cellular oxidants, expressed as the peak change in fluorescence.

	PI	Oxidative burst	CD16	CD32	CD64	CD14
Neutrophils						
Nil	7791(806)	34(17)	84(21)	108(6)	18·1(2·4)	—
LCTs	6743(525)	126(52)	88(22)	109(6)	20·4(2·5)	—
MCTs	6337(597)*	160(131)	24(3)*	104(8)	26·8(5·7)	—
Monocytes						
Nil	5449(648)	14(12)	10·5(1·9)	101(11)	42·8(5·5)	390(76)
LCTs	4625(633)	104(53)	11·2(1·6)	95(8)	42·0(2·9)	366(80)
MCTs	4094(443)*	64(37)	6·6(0·6)*	93(7)	45·5(5·5)	34(27)*

*$P < 0{\cdot}05$ *versus* control (Student's paired t test)

Thus, MCT-containing lipid emulsions influence the functional status of leucocytes, but affect the expression only of phosphatidyl–inositol–glycan-linked receptors. The cellular effects of these lipid emulsions demand more detailed analysis to determine the metabolic basis of their clinical value.

In vitro modulation of natural cytotoxicity by nitric oxide synthetase inhibitors

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The amino acid L-arginine has well known immunostimulatory properties. It was previously shown that L-arginine supplementation (30 g daily for 3 days) increased natural killer (NK) and lymphokine-activated killer (LAK) cell cytotoxicity significantly in 16 patients with locally advanced breast cancer (mean increase 81 and 107 per cent respectively; $P < 0{\cdot}001$). Although L-arginine is a known precursor of the nitric oxide (NO) pathway, its exact mode of action is unclear. In this study the *in vitro* effect of NO synthetase inhibitors *N*-nitro-arginine (NNA) and *N*-methyl-arginine (NMA) on the NK and LAK cell cytotoxicity of peripheral blood lymphocytes (PBLs) from patients with breast cancer was assessed.

In medium containing 1·14 $\mathrm{mmol\,l^{-1}}$ L-arginine (RPMI 1640), LAK cell activity was significantly reduced by 1 $\mathrm{mmol\,l^{-1}}$ NNA or 10 $\mathrm{mmol\,l^{-1}}$ NMA. NK cell activity was significantly reduced only by prior incubation in medium containing 0·1 $\mathrm{mmol\,l^{-1}}$ L-arginine and 1 $\mathrm{mmol\,l^{-1}}$ NNA or NMA.

	Percentage reduction in activity	
	NK (72 h)	LAK (92 h)
NNA	32*	29*
NMA	26*	32†

*$P < 0{\cdot}05$, †$P = 0{\cdot}002$ *versus* controls (log-transformed data, paired t test)

Results are expressed as the mean percentage decrease in cytotoxicity at a ratio of 40:1 (effector:target cells). Similar results were also seen using PBLs from healthy volunteers.

This study shows that NO production from L-arginine is essential for optimal natural cytotoxicity.

Neutrophil response to endotoxin is downregulated in obstructive jaundice

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Neutrophil function in the control of infection depends on the expression of adhesion molecules on the cell surface; these are induced by stimulants, including endotoxin. As patients with obstructive jaundice are prone to septic complications, adhesion molecule expression was examined in nine jaundiced patients (median age 77 (range 29–91) years) and eight controls (median age 50 (range 23–81) years).

Blood was incubated with fluorescein-conjugated monoclonal antibodies to adhesion molecules and the effect of stimulation with endotoxin analysed by flow cytometry.

	Control	Jaundice	Control plus endotoxin	Jaundice plus endotoxin
CD11a	46·8 (42–71)	33·9 (20–47)*	55·5 (42–62)	38·5 (19–50)†
CD11b	22·2 (11–75)	34·6 (11–76)	88·6 (63–122)	66·3 (33–97)†
CD11c	7·6 (5–12)	10·1 (5–17)	22·6 (15–30)	17·2 (7–23)
CD15	229 (124–636)	100 (56–242)*	327 (173–745)	131 (74–268)†

Values are median (range) channel fluorescence. CD, cluster designation. *$P < 0{\cdot}05$ *versus* control; †$P < 0{\cdot}05$ *versus* control plus endotoxin

Basal expression of CD11c and CD15 was lower in jaundiced patients and the response to endotoxin of all the adhesion molecules was attenuated compared with values in the control group. The downregulated response may be due to chronic endotoxaemia, which is known to occur in jaundiced patients, and may in part explain the level of septic complications in patients with obstructive jaundice.

Role of platelet-activating factor in a model of acute pancreatitis

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Platelet-activating factor (PAF), a bioactive phospholipid that has effects on capillary permeability, was investigated for its role in the pathogenesis of acute pancreatitis by administration of BB-882, a selective PAF antagonist.

Pancreatitis was induced by microvascular ischaemia in 24 Wistar rats, creating increases in serum pancreatic enzymes, pancreatic weight and histological evidence of acute pancreatitis. Histological changes were assessed using an established point scoring system for each of the features of oedema, inflammatory infiltrate, fat necrosis, parenchymal necrosis and haemorrhage. Treatment with BB-882, 5 $\mathrm{mg\,kg^{-1}}$ intraperitoneally 30 min after induction of pancreatitis, significantly inhibited elevation of serum amylase concentration and histological changes of pancreatitis.

	Pancreatitis plus saline	Pancreatitis plus BB-882	P*
Serum amylase (units $\mathrm{l^{-1}}$)	3928 (2800–5900)	2477 (2100–3280)	<0·001
Pancreatic weight (g)	2·35 (1·75–3·08)	2·39 (1·92–2·96)	n.s.
Histology score (0–27)	12·3 (8–18)	5 (3–10)	<0·001

Values are mean (range). *Wilcoxon rank sum test; n.s., not significant

PAF may be released endogenously during the evolution of acute pancreatitis. Administration of BB-882, an ethyl ester with specific anti-PAF activity, alters the progression of acute pancreatitis induced in this model.

Circulating intact parathyroid hormone levels in acute pancreatitis

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Proteolytic degradation of parathyroid hormone (PTH) has been demonstrated in the serum from patients with severe acute pancreatitis. It has been suggested that this may contribute to the hypocalcaemia seen in this conditions. Previous studies investigating the parathyroid response in acute pancreatitis have been criticized for using traditional immunoassays that may detect inactive PTH fragments in addition to the intact molecules.

Forty patients with prognostically severe acute pancreatitis had serial measurement of serum calcium, phosphate and PTH levels. PTH was assayed using a two-site immunometric assay specific for the intact molecule.

Sixteen patients developed complications, of whom eight died. PTH levels during the first 3 days of admission were significantly higher in patients with a complicated or fatal outcome than in those with an uncomplicated course (day 1, $P=0{\cdot}003$; day 2, $P=0{\cdot}003$; day 3, $P=0{\cdot}014$, Mann–Whitney U test). Thirteen patients developed hypocalcaemia (adjusted calcium level $<2{\cdot}00\,\text{mmol}\,\text{l}^{-1}$), eight with a complicated and five with an uncomplicated outcome ($P=0{\cdot}114$, Fisher's exact test). Inappropriately low levels of intact PTH ($<5\,\text{pmol}\,\text{l}^{-1}$) were detected in five of these patients, of whom four were in the uncomplicated group.

It is concluded that high levels of intact PTH are found early in the course of acute pancreatitis and are associated with a poor prognosis. It remains to be determined why some patients develop hypocalcaemia without an appropriate rise in the level of PTH.

Pathophysiological studies of postoperative bilious vomiting

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Despite perioperative fasting, bile vomiting is a common postoperative complication that may lead to pulmonary aspiration; its pathophysiology is obscure.

This study sought to determine: (1) enterogastric bile reflux by prolonged intragastric pH monitoring; and (2) causal motor activity by prolonged gastric, duodenal and jejunal manometry in 13 patients both before operation and for 24 h after cholecystectomy. Motility alone was evaluated in three further patients.

Preoperative studies demonstrated stable pH and normal motility in all subjects. Gastric pH was higher after operation than before operation (mean(s.e.m.) pH 4·7(0·5) *versus* 2·9(0·4) respectively; $P<0{\cdot}01$, paired t test) and abnormal motor patterns comprising frequent incoordinate contraction bursts were observed in all patients. Phasic bursts that migrated retrogradely (RPBs) were associated with bile vomiting (35 RPBs occurred in nine vomiters *versus* seven in seven non-vomiters; $P<0{\cdot}05$, paired t test). Intragastric pH fell after bile vomiting episodes (mean(s.e.m.) pH 5·2(0·5) before *versus* 4·8(0·4) after vomiting; $P<0{\cdot}05$, paired t test).

In conclusion, RPBs are the principal motility abnormality associated with postoperative bilious vomiting, probably by inducing enterogastric bile reflux. Postoperative motility disturbances are accompanied by a rise in intragastric pH which falls after episodes of bile vomiting.

Nitric oxide inhibition maintains vasopressin-induced hepatic vasoconstriction

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Hepatic parenchymal vasoconstriction is thought to increase cytotoxic drug uptake into hepatic metastases. However, prolonged infusion of the vasoconstrictor vasopressin does not lead to prolonged vasoconstriction. This study assessed whether loss of vasopressin-induced vasoconstriction is mediated by the endogenous vasodilator nitric oxide (NO).

Hepatic perfusion was monitored by laser Doppler flowmetry in 23 Chester Beatty Hooded rats. Vasopressin ($0{\cdot}5\,\mu\text{g}\,\text{min}^{-1}$) was infused into the hepatic circulation via the gastroduodenal artery in eight animals. In a further seven rats the vasopressin was infused with the NO inhibitor L-nitro-arginine methyl ester (L-NAME). Hepatic perfusion was also measured in eight control animals receiving either L-NAME alone or saline.

Prolonged vasopressin infusion alone produced a reduction >50 per cent in hepatic perfusion, which returned to the preinfusion level within 20 min in all animals. When L-NAME was administered concurrently with vasopressin, a reduction >50 per cent in perfusion was again noted but, unlike the case with vasopressin alone, this lasted >30 min in all animals ($P<0{\cdot}05$). A fall >50 per cent in hepatic perfusion was not noted in any control animal. Furthermore, tachyphylaxis to vasopressin was reversed by the administration of L-NAME.

It is concluded that vasopressin-induced tachyphylaxis is mediated by NO.

Propranolol reduces portosystemic shunting

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Propranolol reduces the risk of variceal haemorrhage. The mechanism of action is unclear, since portal pressure does not always fall, although a reduction in azygos flow is typical, suggesting an action on collateral flow. Azygos flow is an invasive technique and measures only one aspect of shunting. Using the systemic availability of low-dose oral galactose to quantify shunting, the effects of chronic β-blockade were assessed.

Ten patients with portal hypertension were entered into a prospective double-blind placebo-controlled crossover trial. Portosystemic shunting, galactose clearance (an index of hepatic flow), galactose excretion capacity (GEC) and modified Child's grade were assessed. Patients underwent repeated measurements at monthly intervals while receiving propranolol 80 mg or placebo. Results were analysed using the Mann–Whitney U test.

Shunting was significantly reduced ($P=0{\cdot}021$) following administration of propranolol. Clearance was not significantly altered ($P=0{\cdot}59$).

	Shunting (%)	Clearance ($\text{l}\,\text{min}^{-1}$)
Propranolol	39·1	0·88
Placebo	70·8	1·03

The reduction in shunting did not correlate with either the GEC or Child's grade.

In conclusion, a reduction in shunting with unaltered hepatic flow suggests a direct action on collateral tone. This may explain the lack of portal hypotensive effect of propranolol in some patients. The alteration in shunting is not dependent on the degree of hepatic decompensation.

Liver function and splanchnic blood flow in critically ill patients

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Hepatic dysfunction is common in critically ill surgical patients and is causally related to multiple organ failure. Splanchnic ischaemia may be important. The aim of this study was to assess hepatic function and blood flow in these patients using two dynamic tests (indocyanine green (ICG) clearance and lignocaine metabolism to monoethylglycinexylidide (MEGX)), to compare them with standard liver function test results and to relate them to measurements of gastric intramucosal pH (pH_{im}), which vary with splanchnic blood flow. Ethical committee approval was obtained.

In all, 27 patients (median 24-h Acute Physiology and Chronic Health Evaluation II score 22) were studied for 3 days following admission to the intensive care unit. Measurements were made of ICG clearance, MEGX formation, serum levels of bilirubin; transaminase and alkaline phosphatase, and pH_{im}.

There were no significant differences between non-survivors and survivors in any parameter except for MEGX levels on day 3 (2·4 *versus* $16\,\text{ng}\,\text{ml}^{-1}$ respectively, $P<0{\cdot}001$) and pH_{im} on days 2 and 3 (7·26 *versus* 7·37, $P<0{\cdot}05$, and 7·14 *versus* 7·40, $P<0{\cdot}001$, respectively). Both MEGX concentration and pH_{im} fell significantly in non-survivors over the 3 days (from 20·6 to $2{\cdot}4\,\text{ng}\,\text{ml}^{-1}$, $P<0{\cdot}002$, and from 7·34 to 7·14, $P<0{\cdot}01$, respectively). MEGX levels and pH_{im} were significantly correlated ($r_s=0{\cdot}69$, $P<0{\cdot}001$).

The metabolism of lignocaine to MEGX depends on both liver blood flow and hepatocellular function, and this test provides a dynamic assessment of hepatic function in critically ill patients. This study suggests that hepatic dysfunction is related to reduced splanchnic blood flow and oxygenation, and therefore improvement of splanchnic blood flow may improve both hepatic function and outcome.

Defective mucin response to *Helicobacter pylori* infection in patients with duodenal ulcer

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Helicobacter pylori is implicated in the pathogenesis of both peptic ulcer and non-ulcer dyspepsia. Decreased mucin synthesis alters the balance between mucosal protection and acid–pepsin damage. The aim of this study was to measure the effect of *H. pylori* infection on 24-h gastric mucosal mucin secretion using a human explant model.

A total of 90 gastric antral mucosal biopsies were taken at upper gastrointestinal endoscopy from 27 patients. Subjects were classified according to endoscopic findings and *Helicobacter* status. Biopsies were incubated in CMRL 1066 medium supplemented with [^{3}H]glucosamine for 24 h. Mucin secreted into the culture medium was measured using a technique based on acid precipitation of the glycoprotein and scintillation counting of incorporated tritiated glucosamine. The quantity of protein in the gastric biopsies was measured using the Lowry method.

Endoscopy *H. pylori*	Normal Negative	Normal Positive	Gastritis Negative	Gastritis Positive	Duodenal ulcer Positive
No. of patients	8	4	3	6	6
No. of biopsies	23	16	13	21	17
Mucin secretion*	1096(135)	1563(137)	954(108)	2158(381)	952(99)

*Values are mean(s.e.m.) disintegrations per min per μg protein

Significantly increased mucin production occurred in response to *H. pylori* infection in patients with and without gastritis ($P<0{\cdot}002$, analysis of variance). This did not occur in patients with duodenal ulceration ($P>0{\cdot}01$), indicating a defective mucosal protective response that may result in ulceration.

Treatment of patients with perforated peptic ulcer for *Helicobacter pylori* infection

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Perforated peptic ulcers are well treated by simple surgical closure. However, ulcers persist in at least 30 per cent of patients. This study looked at a possible aetiological agent, *Helicobacter pylori*, in peptic ulcer disease and its relationship to ulcer perforation and persisting ulcer.

Twenty-nine patients with perforated ulcers were studied. [^{13}C]urea breath tests (^{13}C-UBTs) were performed on day 8 after surgery. Of the 29 patients, 17 underwent upper gastrointestinal endoscopy 6 weeks after discharge.

All patients underwent simple ulcer closure and none received antibiotics in the postoperative period. Twenty-four patients had positive ^{13}C-UBT results. Of the 17 patients who underwent postoperative endoscopy, 14 had positive ^{13}C-UBT results, seven a duodenal ulcer, ten duodenitis or gastritis or both, and one a deformed duodenum. Twelve of the 14 patients with a positive breath test result also had a positive biopsy urease (CLO) finding at the time of endoscopy, indicating the presence of *H. pylori*. None of the patients with a negative ^{13}C-UBT result had evidence of active ulceration, but one had a positive CLO test result.

H. pylori infection is commonly found in patients with perforated peptic ulcer and consideration should be given to prescribing treatment designed to eradicate this infection in all patients after simple perforation closure.

Spontaneous basement membrane formation development in a tissue-culture graft

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An essential prerequisite of a small-diameter vascular graft is that the luminal surface should be non-thrombogenic. Seeding of synthetic grafts with long-term adherence of endothelium has not been achieved, primarily because of the failure of the attachment factors used.

Smooth muscle cells obtained from the vein of a 65-year-old man were serially cultured. At second passage they were added to a $1{\cdot}0\,\mathrm{mg\,ml^{-1}}$ type I collagen gel and cast on to Dacron. Endothelium derived from the same vein was seeded at a concentration of $5\times10^4\,\mathrm{cells\,cm^{-2}}$ on day 17 on to the collagen and left for 7 days.

Histological sections revealed a monolayer of factor VIII-positive endothelium tightly adherent to the underlying collagenous matrix populated by smooth muscle cells. Immunocytochemical staining showed the presence of the basement membrane proteins laminin and type IV collagen throughout the cytoplasm and on the periphery of the endothelium. Mechanical abrasion inflicted on the endothelialized surface was confirmed by scanning electron microscopy to be completely healed at 7 days.

In conclusion, cells that produce their own basement membrane proteins behave more like endothelium *in vivo* and may be more adherent to grafts than those seeded on to synthetic surfaces by artificially applied attachment factors.

Indocyanine green potentiation of laser–tissue interaction

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Palliation of gastrointestinal malignancy by neodymium yttrium–aluminium–garnet (NdYAG) laser therapy is a well established technique. Enhanced tissue destruction may be possible using an 805-nm diode laser with potentiation of laser–tissue interaction by intravenous indocyanine green (ICG), a water-soluble tricarbocyanine dye with a peak spectral absorption at 800–810 nm in blood and plasma. Studies on the possible potentiation of 805-nm diode laser–tissue interaction were carried out *in vivo* on rat liver.

Using a 600-μm bare fibre in non-contact mode with a distance of 1 cm between fibre and tissue, thermal injury was produced at a power of 20 W applied for 2 s with laser energy at 805 and 1064 nm. The extent of thermal tissue destruction was then assessed.

ICG dose ($\mathrm{mg\,kg^{-1}}$)	Diameter of thermal injury 5 min after ICG (mm) 805 nm	 1064 nm
0	4·19 (3·25–5·12)	3·85 (3·33–4·37)
0·1	3·13 (2·25–4·01)	3·08 (2·53–3·62)
1·0	5·90 (5·38–6·42)*	3·06 (2·71–3·42)
10·0	7·38 (6·74–8·01)†	2·99 (2·56–3·41)

Values are median (95 per cent confidence interval). *$P<0{\cdot}005$, †$P<0{\cdot}0001$ *versus* control

Potentiation also occurred at all powers in the range 5–25 W at a dose of $1\,\mathrm{mg\,kg^{-1}}$ ICG. There was no potentiation of NdYAG activity.

Intravenous ICG potentiated 805-nm diode laser–tissue interactions in this model. The 805-nm diode laser with ICG potentiation may enhance gastrointestinal tumour destruction.

Modulation of cytotoxic drug accumulation into human tumour cell lines and explanted cultures by essential fatty acids

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Endeavour to achieve improved efficacy while minimizing the dose-related side-effects of cancer chemotherapy fuels the search for response-modifying agents. Using flow cytometry to measure cellular levels of intrinsically fluorescent anthracyclines, the modifying effects of the essential fatty acids (EFAs) γ-linolenic acid (GLA) and eicosapentaenoic acid (EPA) on drug accumulation in human cancer cells were studied.

Human colorectal (HT29) and breast (MCF7) cancer cell lines and primary cultures from human bladder transitional cell carcinoma (TCC) biopsies ($n = 11$) were grown *in vitro*. Following 24-h pretreatment with EFAs at pharmacologically achievable doses (25–50 μg ml^{-1}), cells were exposed to mitozantrone (for MCF7), Adriamycin (for HT29) and epirubicin (for TCC) at clinically relevant doses for 1 h. Cells were enzymatically disaggregated and read live by flow cytometry.

A highly significant increase in drug accumulation was seen in cells modified by lipids, specifically HT29 modified with EPA and MCF7 with GLA. EPA at high dosage ($>100\,\mu$g ml^{-1}) also enhanced drug accumulation for MCF7. Bladders responded to both EFAs and exhibited intratumour and intertumour variability.

	HT29	MCF7	TCC
Control	9·3(1·5)	15(5)	43·8(8)
Drug	149·7(4)	109(10)	240(150)
Drug plus EPA	185(7)	107(15)	1240*
Drug plus GLA	145(15)	151(20)	

Values are mean(s.d.). *Increase 2–800-fold

The addition of EFAs alone did not change control values.

Clostridium perfringens α-toxin in acute gastrointestinal inflammation

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Some examples of intra-abdominal tissue necrosis may be the result of locally produced toxin at the site of bacterial multiplication rather than the result of vascular infarction. *Clostridium perfringens* is present in the gastrointestinal tract of a large proportion of the population. The type A strain produces α-toxin (phospholipase C), which has the ability to degrade cell membranes directly, leading to cell necrosis. *C. perfringens* α-toxin has been measured by sandwich enzyme-linked immunosorbent assay in the serum of patients presenting as acute abdominal emergencies.

	No. of patients	Mean(s.e.m.) toxin level (assay units)	*P*
Control patients	22	5(6)	
Acute biliary disease	18	137(18)	<0·00001
Acute appendicitis	12	123(24)	<0·00001
Acute pancreatitis	21	81(38)	0·051
Colonic perforation	12	144(20)	<0·00001

In acute biliary disorders, appendicitis and colonic perforation, very high levels of toxin were detected ($P<0{\cdot}00001$). The highest individual level (772 units) was in a patient with acute pancreatitis but, as a group, levels of toxin in patients with pancreatitis were not statistically significantly raised ($P=0{\cdot}051$).

Raised levels of toxin in acute biliary disorders and appendicitis support the hypothesis that *C. perfringens* infection may be a factor in the pathogenesis of these conditions. High levels of toxin in some patients with acute pancreatitis may be of importance in view of the progression of this condition to necrotizing pancreatitis.

Somatostatin analogue inhibits tumour growth in regenerating liver

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Since tumour growth is enhanced by partial hepatectomy and because octreotide inhibits the growth of experimentally induced hepatic tumours, the effects of octreotide on tumour growth in the regenerating liver were investigated.

Hepatic tumour was induced by the intraportal injection of HSN cells (fibrosarcoma) or K12-Tr cells (adenocarcinoma) into Hooded Lister (HL) and BDIX rats respectively, immediately after a 70 per cent hepatectomy. The hepatectomized rats received either octreotide 2 μg subcutaneously twice daily or the same volume of saline for 3 weeks, after which time the percentage hepatic replacement (PHR) of liver by tumour was calculated.

PHR was significantly reduced in octreotide-treated animals compared with saline-treated rats ($P<0{\cdot}001$, Mann–Whitney *U* test). In the HL–HSN model, the median PHR of 71·3 (range 32·3–85·7) was reduced to 8·4 (0–22·1) by octreotide, and in the BDIX–K12-Tr model from 38·3 (29·1–42·6) to 4·5 (0·04–7·7).

The results of this study suggest that octreotide inhibits tumour growth in the regenerating liver and that it may have a role as an adjuvant following liver resection for hepatic metastasis or hepatoma.

Loss of bombesin receptor G-protein linkage in human colonic cancer cells

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Human gastric and colonic cancer cell lines are known to express receptors for the mitogenic bombesin family peptide gastrin-releasing peptide (GRP). Cloning of the GRP receptor from Swiss 3T3 fibroblasts has demonstrated it to be a member of the seven-transmembrane domain superfamily, which activate second messenger systems via guanine nucleotide-binding regulatory proteins (G proteins). It has been proposed that the *ras* oncogene product, p21, is the G protein by which the GRP receptor activates phospholipase C.

The aim of the study was to determine G-protein linkage of GRP receptors on membrane preparations from human gastric (St42) and colonic (COLO320HSR) cancer cell lines by assessing the ability of a non-hydrolysable GTP analogue, guanosine-5′-*O*-3-thiotriphosphate (GTP-γ-S) (10^{-8}–10^{-4} mol l^{-1}), to inhibit specific binding of ^{125}I-labelled Tyr^{4}-bombesin.

Results showed that GRP receptors on St42, but not those on COLO320HSR, are G-protein linked.

	IC$_{50}$ for GTP-γ-S(mol l^{-1})
St42	2×10^{-7}
COLO320HSR	$>1 \times 10^{-4}$

IC$_{50}$, mean inhibitory concentration

In conclusion, loss of G-protein linkage of the GRP receptor has occurred in COLO320HSR but not in St42 cell lines. A *ras* mutation, which is common in patients with colorectal carcinoma but uncommon in those with gastric cancer, is the most likely explanation for the finding. This loss of linkage may result in permanent activation of the 'downstream' signal transduction pathway, thus contributing to the uncontrolled proliferation found in colorectal cancer cells.

Streptokinase inhibits experimental pulmonary seeding without significant systemic fibrinolysis

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The haemostatic system plays an important role in the metastatic process. Fibrin and platelets are often found around tumour emboli and may aid tumour adhesion to the endothelium of target organs. The aim of this study was to investigate the dose-related effects of streptokinase (SK) on the coagulation system and to assess its efficacy as an antimetastatic agent in a rat model of metastasis.

Four groups of five female F344 rats were given different doses of SK or saline (control) intravenously. Blood was taken for estimation of thrombin time (TT) and fibrin plate lysis assay (FPLA) after 30 min.

	Dosage of SK (units kg^{-1})			
	0	15 000	30 000	45 000
TT (s)	47·8(6·5)	42·4(1·1)	409·8(38·2)	528(123·3)
FPLA (mm)	4·76(0·10)	4·44(0·19)	7·70(0·43)	8·92(0·54)

Values are mean(s.e.m.)

Four groups of seven female F344 rats were given 10^{5} Mtln3 cells intravenously, together with different doses of SK or saline (control). Animals were killed at 17 days and pulmonary nodules assessed.

	Dosage of SK (units kg^{-1})			
	0	5000	15 000	30 000
No. of lung nodules	49·1(2·5)	33·6(2·3)*	29·4(2·7)†	22(2·4)†

Values are mean(s.e.m.). *P=0·0012, †P=0·0006 *versus* control (Mann–Whitney U test)

The effect of SK on pulmonary seeding was dose related and significant in the absence of detectable systemic fibrinolysis. Reduction of seeding from circulating tumour cells following administration of SK may therefore be applicable in the perioperative period.

Mammographic microcalcification predicts resection margin involvement in screening breast biopsies

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The presence of tumour either at the resection margin or in the shavings of a malignant breast biopsy continues to pose therapeutic management problems.

The surgical and pathological results of 244 women from the authors' screening practice have been studied, 120 with and 124 without mammographic microcalcification (MM); 49 were found to have ductal carcinoma *in situ* (DCIS) and 195 invasive malignancy. Of those with MM, 83 (69 per cent) of 120 were shown to have tumour at the resection margin of the breast biopsy. Of the 49 patients with DCIS, 34 biopsies showed involved margins; significantly, 11 of 12 patients with multifocal DCIS had residual disease at further surgery compared with only seven of 22 with unifocal disease (P=0·003, χ^2 test). Of women with invasive malignancy, 49 (69 per cent) of 71 with MM compared with 54 (44 per cent) of 124 without had tumour at the resection margin (P=0·0001, χ^2 test). When the re-excised specimen was examined, 25 (35 per cent) of 71 specimens from patients with MM and 24 (19 per cent) of 124 without MM contained residual tumour.

	Margins involved	Residual re-excision disease	
		DCIS	Invasive
MM			
Present (n=120)	83	35	8
Absent (n=124)	54	13	11

In all cases (DCIS plus invasive malignancy) the presence of MM indicated that resection margin involvement with tumour was likely (P=0·0001), and that the re-excision specimen would probably contain residual disease (P=0·006). These observations were independent of tumour size and axillary node status.

The presence of microcalcification on the screening mammogram therefore indicates that a wider than usual surgical resection margin should be employed.

Cytotoxic drug fluorescence in human cancer cell lines: a model for drug sensitivity assays in tumour chemotherapy

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Adjuvant chemotherapy for most human solid tumours is arbitrary and empirical. Direct measurement of cytotoxic drug levels in cells might improve therapeutic drug monitoring. The intrinsic fluorescence of anthracycline-related drugs allows a simple and direct assay in cells, using conventional flow cytometry.

The authors have developed such an assay in human cancer models. Breast (MCF7) and colon (HT29) cell lines growing as monolayers were exposed to serial concentrations of Adriamycin and mitozantrone (MTZ). Disaggregated cells were transferred on ice for immediate assay (FACScan, FL3 detector) or viably frozen.

Drug accumulation was directly proportional to the external concentration up to 7 μg ml^{-1} for Adriamycin and 10 μg ml^{-1} for MTZ, saturating thereafter. Immediate (surface) binding represented 5 per cent of the total at 1 h. Fluorescence was conserved in live cells recovered from nitrogen. Drugs were measurable in cells exposed to estimated clinical extracellular concentrations, as supported by the demonstration of *in vivo* accumulated drug in blood leucocytes from patients with leukaemia (fluorescence equivalent to 1·5–5 μg ml^{-1} *in vitro* exposure).

	MTZ in MCF7 (μg ml^{-1})							
	0	1	2	5	12·5	25	50	100
F13 channel fluorescence	7(2·2)	27(3·9)	56(12)	139(16)	201(17)	263(47)	326(56)	395(65)

Values are mean(s.d.)

These results form the basis for detailed studies of cytotoxic accumulation in clinical material. They should encourage a re-evaluation of adjuvant treatment schedules using a sensitive direct flow cytometric assay of target cells.

Thrombotic mediators and prediction of early outcome following reconstructive vascular surgery

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A total of 204 patients undergoing reconstructive vascular surgery have been studied prospectively to determine the relationship between potential thrombotic mediators and poor early postoperative outcome (hospital mortality or graft occlusion).

In 30 patients with a poor outcome following surgery (11 deaths, 19 graft occlusions), preoperative levels of fibrin degradation products (FDPs), fibrinogen and von Willebrand Factor (vWF) were raised and factor VII levels reduced compared with values in patients with a good postoperative outcome (P<0·005, Mann–Whitney U test).

	Good outcome	Poor outcome	P*
Fibrinogen (g l^{-1})	3·5 (2·9–4·4)	4·8 (4·4–5·5)	0·000002
FDPs (ng ml^{-1})	175 (104–344)	332 (220–532)	0·0005
vWF (units dl^{-1})	140 (99–182)	262 (199–349)	<0·000001
Factor VII (%)	106 (92–118)	91 (72–103)	0·004

Values are median (interquartile range). *Mann–Whitney U test

Poor outcome was more common in patients with critical limb ischaemia. Median age was similar in both groups, and there were no significant differences in concurrent pathologies between the two groups, with the exception of diabetes mellitus.

It is suggested that preoperative evaluation of thrombotic variables may enable the detection of high-risk patients. Further studies are required to develop a predictive index for poor outcome.

Cost–effectiveness of prophylaxis of deep vein thrombosis in general surgery

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A meta-analysis was performed on published studies in which objective diagnostic tests had been used to determine the overall efficacy of methods of prophylaxis of deep vein thrombosis (DVT).

In 3848 patients (50 studies) belonging to control groups, the incidence of DVT was 21·2 per cent (95 per cent confidence interval (c.i.) 19·9–22·4 per cent). When graduated elastic compression (GEC) was used (ten studies, 863 patients), the incidence of DVT was 13·6 per cent (95 per cent c.i. 11·1–15·6 per cent). When intermittent pneumatic compression (IPC) was used (11 studies, 601 patients), the incidence was 6·8 per cent (95 per cent c.i. 4·8–8·8 per cent). With low-dose heparin (LDH) (59 studies, 7092 patients), the incidence was 8·1 per cent (95 per cent c.i. 7·1–8·7 per cent). When low molecular weight heparin (LMWH) was used (18 studies, 3558 patients), the incidence was 5·6 per cent (95 per cent c.i. 4·8–6·3 per cent).

Subsequently, the cost of 7-day treatment with each method was calculated. It was £5·94 for GEC, £6·58 for IPC, £16·80 for LDH and £38·00 for LMWH. On the basis of this, the cost of prophylaxis per 1000 patients for each prophylactic method has been calculated. The cost of every prophylactic method has been found to be less than the cost of no prophylaxis (i.e. cost for diagnostic investigations and treatment of those who develop clinical DVT), indicating that not only is DVT prevented but also that money is saved. The saving to the hospital per 1000 patients was approximately £3000 for LDH and £13 000 for IPC.

These figures should be borne in mind when units or hospitals plan their policy on prophylaxis of DVT.

Lovastatin reduces the proliferation of vascular smooth muscle cells by inhibiting isoprenoid but not cholesterol synthesis

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The inhibition of restenosis resulting from myointimal hyperplasia remains an unsolved problem following vascular intervention. Lovastatin is an inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase and has been found to reduce the incidence of restenosis in several animal models and in one human coronary restenosis trial. Its effect on cultured human vascular smooth muscle cells (VSMCs) ($n = 18$) was examined.

Growth rates of subcultured VSMCs were assessed by counting at 0, 3, 7, 10 and 14 days and the effects of adding lovastatin, mevalonate and cholesterol measured.

	Mean(s.e.m.) inhibition at 14 days (%)
Lovastatin (2 μmol l^{-1})	37(4)
Lovastatin plus mevalonate (400 μmol l^{-1})	0
Lovastatin plus cholesterol (10 μg ml^{-1})	36(2)

In separate experiments, [^{3}H]thymidine (^{3}H-T) uptake (an index of DNA synthesis) was measured, as well as the effects of the isoprenoids farnesol and isopentenyl adenine.

	Mean(s.e.m.) inhibition of ^{3}H-T uptake (%)
Lovastatin (10 μmol l^{-1})	48(3)
Lovastatin plus mevalonate (400 μmol l^{-1})	14(2)
Lovastatin plus farnesol (10 μmol l^{-1})	20(2)
Lovastatin plus isopentenyl adenine (50 μmol l^{-1})	48(3)
Lovastatin plus cholesterol (10 μg ml^{-1})	40(4)

The antiproliferative effects of lovastatin are prevented by mevalonate (the product of HMG-CoA reductase) but not by cholesterol ($P < 0·001$, Mann–Whitney U test). Furthermore, the mevalonate metabolite farnesol also reduces the effect ($P < 0·01$, Mann–Whitney U test), but not the isoprenoid end-product isopentenyl adenine, suggesting that lovastatin inhibits VSMC proliferation by depleting farnesol.

Further *in vitro* investigation of lovastatin as a possible therapeutic agent in restenosis is warranted.

Quality of life after infragenicular bypass

R.D. Sayers, M.M. Thompson, A. Reid, M.J. Underwood, D.A. Ratliff and P.R.F. Bell, *Department of Surgery, University of Leicester, Leicester, UK*

Infragenicular bypass may achieve high rates of limb salvage, but little attention has been directed towards the functional results of this procedure. The aim of this study was to assess the quality of life after femorodistal bypass objectively and to compare it with the quality of life achieved following primary limb amputation.

A self-assessment postal questionnaire containing scales measuring emotional disorder, social functioning and mobility was sent to 112 patients who had previously undergone femorodistal bypass ($n = 86$) or primary limb amputation ($n = 26$). The response rate was 94 per cent. The results are presented as median (95 per cent confidence interval); the lower the numerical value, the higher the quality of life.

	Maximum possible score	Femorodistal bypass	Primary amputation	P*
Anxiety	21	6 (5–7)	9 (6–10)	>0·1
Depression	21	6 (4–8)	9 (5–11)	<0·05
Social function	30	9 (7–11)	16 (10–19)	<0·01
Immobility	4	2 (1–2)	4 (2–4)	<0·01

*Mann–Whitney U test

Further analysis demonstrated that a secondary procedure (percutaneous transluminal angioplasty or graft revision) to maintain graft patency did not adversely affect the quality of life. Additionally, patients undergoing secondary amputation after graft failure had an identical quality of life to those undergoing primary amputation.

These data illustrate that the quality of life after successful femorodistal bypass is higher than after primary or secondary amputation. To attain the maximum quality of life in patients with critical ischaemia, femorodistal bypass should be performed whenever feasible.

Restoration of the endothelial monolayer decreases intimal hyperplasia after vascular reconstruction

M.M. Thompson, J.S. Budd, S. Eady, R.F.L. James and P.R.F. Bell, *Department of Surgery, University of Leicester, Leicester, UK*

Myointimal hyperplasia develops as a generalized response to vascular injury and may cause stenoses in 40 per cent of all peripheral arterial reconstructions. Disruption of the endothelial monolayer is a prerequisite for the development of intimal hyperplasia (IH) and may be the initiating event in the process. This study examined the hypothesis that restenosis following balloon angioplasty may be reduced by rapid restoration of the endothelial monolayer, achieved by endothelial seeding.

Bilateral iliac angioplasty was performed in 11 rabbits. A double-balloon catheter was used to seed one angioplasty site with autogenous endothelial cells; the contralateral site was sham seeded with culture medium and acted as a control. Arterial patency rates, the degree of IH, expressed as the ratio of the neointimal area to the normalized area enclosed by the internal elastic lamina (IEL), i.e. IH:IEL, and the extent of endothelialization were quantified at 1 ($n = 5$) and 3 ($n = 6$) weeks following balloon dilatation. Results from both time periods are presented as median (95 per cent confidence interval (c.i.)).

	Endothelial seeded	Control site	Difference (95% c.i.)
Patency rate (%)	100	64	1·0–53·6*
IH:IEL (%)	8·1 (0–17)	19·5 (5–28)	1·5–11·5†
Endothelialization (%)	64 (12–83)	0 (0–33)	10·5–62·5†

*χ^2 test; †Wilcoxon paired rank test

The data suggest that transluminal endothelial seeding may be a therapeutically applicable technique as it decreases myointimal hyperplasia and increases patency following angioplasty. This study also illustrates the protective effect of the vascular endothelium following arterial injury and indicates that intensive efforts should be made to preserve the endothelium during vascular reconstruction.

Human venous endothelium can promote intimal hyperplasia via a paracrine mediator

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Current theories on the aetiology of intimal hyperplasia invoke a central role for both endothelial and smooth muscle cells. The purpose of this study was to investigate the interaction between these cells using an organ culture system.

Saphenous vein from 30 patients was cultured in RPMI medium supplemented with 30 per cent fetal calf serum. For 20 of the veins, an intact segment and a segment from which the endothelium had been denuded by gentle abrasion were cultured separately. The same protocol was followed for the remaining ten veins, but in addition a co-culture was established comprising an intact and a denuded segment in culture together. After 14 days, intimal thickness was measured using an image analysis system.

The results from the 20 separate cultures showed that the median (range) intimal thickness for the intact veins was 24·5 (6·5–81·0) μm and for the endothelial denuded veins 2·5 (0·0–27·5) μm; this difference was significant ($P = 0{\cdot}0001$). The co-culture studies showed that endothelial-denuded veins cultured alongside intact veins developed significantly more intimal thickening than denuded veins cultured alone (median thickness 12 *versus* 0 μm, $P = 0{\cdot}001$). However, this thickening was less than that of intact segments cultured alone (median thickness 12 *versus* 28 μm, $P = 0{\cdot}01$). It is concluded that intimal hyperplasia of human saphenous vein can be promoted by an endothelium-derived mediator that acts in a paracrine fashion.

Hydrogen clearance as a non-invasive technique for measuring skin blood flow in critical ischaemia

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A new transcutaneous hydrogen (H_2) clearance technique has been developed for measuring skin blood flow (SBF) in patients with critical ischaemia. Measurements were carried out in the forearms of eight normal volunteers (group 1) and in the legs of ten patients with ischaemia (group 2), using protocols approved by the local ethical committee.

After stabilization of a specially prepared, but standard, electrode for measuring the transcutaneous partial pressure of oxygen ($P_{\mathrm{tcO_2}}$) at 40°C on the skin for 10 min, all subjects breathed 2 per cent H_2 in air for 15 min; the clearance was measured subsequently during breathing of room air. In group 1, laser Doppler flux (LDF) measurements (at 40°C) were carried out simultaneously at a neighbouring site. In group 2, ^{125}I-labelled 4-iodoantipyrine (IAP) clearance was measured immediately before and at the same sites as measurement of the transcutaneous partial pressure of H_2 ($P_{\mathrm{tcH_2}}$). The results of comparisons of the methods are given in the *Table*, which shows the regression of H_2 clearance against LDF and IAP: SBF ($P_{\mathrm{tcH_2}}$) = 7·9 LDF + 30·8; SBF ($P_{\mathrm{tcH_2}}$) = 1·39 SBF (IAP) + 6·8.

	No. of results	No. of subjects	r	P	Mean(s.d.) SBF ($P_{\mathrm{tcH_2}}$) (ml per 100 g)	Group
LDF	16	8	0·70	< 0·001	48·0(13·9)*	1
IAP	15	10	0·85	< 0·001	15·7(5·2)	2

*$P < 0{\cdot}001$ *versus* group 2 (Mann–Whitney U test)

There were significant correlations between H_2 clearance and LDF and IAP measurements. A highly significant difference in $P_{\mathrm{tcH_2}}$ SBF values was observed between groups 1 and 2.

Measurement of $P_{\mathrm{tcH_2}}$ is a new, reproducible, non-invasive methodology for assessing SBF. It correlates particularly well with radioisotope clearance, which it may ultimately supersede as the method of choice for assessment of SBF.

Falsely high pressure measurements in lower-limb ischaemia: an alternative approach

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Ankle:brachial pressure indices (ABPIs), measured by sphygmomanometer and Doppler probe, are an accepted index of chronic leg ischaemia. However, tibial artery sclerosis or calcification decreases compliance, producing falsely raised cuff occlusion pressures. Arterial cannulation is invasive and impractical but, by elevating the foot and measuring the height at which the Doppler signal disappears, ankle systolic pressure is easily derived.

Using an 8-MHz Doppler apparatus and calibrated pole, ankle systolic pressures measured by sphygmomanometer and elevation were compared in 49 critically ischaemic legs (40 patients). In 20 legs undergoing vascular reconstruction, direct intra-arterial measurement of ankle systolic pressure was made via transducer. ABPIs were derived by dividing ankle systolic pressure by brachial pressure.

In 49 limbs the mean(s.d.) ABPI measured by cuff differed significantly from that derived by leg elevation (0·51(0·32) *versus* 0·22(0·10), $P < 0{\cdot}001$). In 20 patients studied at operation, the mean ABPI was 0·45 by cuff, 0·20 by elevation and 0·18 by transducer. Correlation of elevation with transducer-assessed pressure measurements ($r = 0{\cdot}88$, $P < 0{\cdot}001$) was closer than that obtained with cuff pressure measurements ($r = 0{\cdot}69$, $P < 0{\cdot}001$).

Pressures derived by leg elevation provide a more accurate index of ischaemia than sphygmomanometry. Falsely high ABPIs may underestimate the extent of disease in patients assessed for vascular reconstruction.

Accelerated peripheral thrombolysis with pulse-spray technique

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Pulse-spray thrombolysis (PST) is a new technique for peripheral thrombolysis. Experience of 24 consecutive patients treated using this technique is presented. Details of patient age, duration of symptoms, length of occlusion and total dose of recombinant tissue plasminogen activator (rtPA) are shown.

Age (years)	74·5 (35–89)
Duration of symptoms (days)	6 (1–60)
Length of occlusion (cm)	23 (4–55)
Dose of rtPA (mg)	18 (10–35)

Values are median (range)

Severe ischaemia with sensory and motor deficit was present in 11 of 24 patients. rtPA was used in a concentration of 0·33 mg ml^{-1} in boluses of 0·2 ml every 30 s. Complete radiological lysis was achieved in 23 of 24 cases and the median duration of lysis was 137·5 (range 35–1125) min. This was an 11-fold reduction and was significantly lower ($P < 0{\cdot}001$, Mann–Whitney U test) than the median lysis time of 1545 (range 330–5760) min found in 120 consecutive patients treated with slow rtPA infusion in the authors' unit. The median ankle:brachial pressure index improved significantly ($P = 0{\cdot}002$, Mann–Whitney U test) from a prelysis value of zero to 0·8 following lysis.

PST rapidly restores vascular patency and may therefore become the treatment of choice in patients with acute limb ischaemia, including those at immediate risk of irreversible ischaemic damage, which would conventionally be treated with emergency surgical reconstruction.

SURGERY ABSTRACTS

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A selection from the October issue of the American journal, which was given over to papers presented at the 50th Annual Meeting of the Central Surgical Association in Cincinatti, Ohio, March 1993.

Awake patient monitoring to determine the need for shunting during carotid endarterectomy

Marshall E. Benjamin, MD, Michael B. Silva, Jr., MD, Cathleen Watt, MD, Michael T. McCaffrey, PhD, Adrienne Burford-Foggs, MD, *and* **William R. Flinn, MD,** *Chicago, Ill.*

Background. *The indications for shunt placement to prevent cerebral ischemia during carotid endarterectomy have been controversial. Some investigators have recommended empiric shunting for patients presumed to be at higher risk for cerebral ischemia with a recent stroke or severe stenosis or occlusion of the contralateral internal carotid artery.*

Methods. *Carotid endarterectomy was performed in 81 cases with cervical block anesthetic, monitoring the awake patient for the development of cerebral ischemia (unresponsiveness or paralysis) during carotid clamping. The need for shunting (based on awake response) was compared in patients with the arbitrarily defined empiric indications for shunting ($n = 29$) versus those who did not have such clinical or anatomic findings ($n = 52$).*

Results. *Cerebral ischemia requiring shunting was observed in five (17.2%) of 29 cases with the defined indications for empiric shunting. This was not different than the need for shunting in the control group where cerebral ischemia was seen in eight (15.4%) of 52 cases. No intraoperative neurologic events occurred in any case, but one (1.2%) patient suffered a postoperative transient ischemia attack and another (1.2%) had a postoperative stroke.*

Conclusions. *Empiric clinical or anatomic indications for shunting were not reliable predictors of cerebral ischemia that developed during carotid clamping in this study. Awake patient monitoring during carotid endarterectomy with regional anesthetic allowed prompt, accurate identification of patients with cerebral ischemia who would clearly benefit from placement of a shunt. (SURGERY 1993;114:673-81.)*

Histocompatibility and liver transplantation

Stuart J. Knechtle, MD, Munci Kalayoglu, MD, Anthony M. D'Alessandro, MD, Beth Mason, BS, John D. Pirsch, MD, Hans W. Sollinger, MD, Daniel C. Steen, RN, *and* **Folkert O. Belzer, MD,** *Madison, Wis.*

Background. *The role of histocompatibility between donor and recipient in liver transplant rejection is unclear because of a paucity of data. The influence of human leukocyte antigen (HLA) type on immunologic graft loss was examined for primary liver transplantations performed at this center.*

Methods. *Immunologic graft loss included patient death or retransplantation as a result of rejection or impending graft loss caused by either late hepatic artery thrombosis or severe, unremitting rejection requiring FK 506 rescue therapy. HLA A, B, and DR matching was available on 205 donor-recipient combinations, and an additional 31 patients had A and B matching only.*

Results. *A mismatch of class I antigens (HLA A and B) was predictive of immunologic graft loss ($p = 0.018$). DR mismatch did not correlate with graft loss. When the A and B loci were analyzed separately, an A mismatch correlated significantly with immunologic graft loss ($p = 0.02$), in contrast to a B mismatch ($p = 0.17$). Better matching significantly improved patient survival ($p = 0.02$) and overall graft survival ($p = 0.009$).*

Conclusions. *The beneficial effect of HLA class I antigen compatibility on liver transplantation outcome is in contrast to pancreatic and kidney transplantation in which class II antigen matching but not class I matching is beneficial. Immunologic mechanisms of hepatic allograft rejection may differ from those involved in kidney transplant rejection. (SURGERY 1993;114:667-72.)*

Two hundred consecutive simultaneous pancreas-kidney transplants with bladder drainage

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Background. *Since 1982, 288 pancreas transplantations have been performed at the University of Wisconsin. This report reviews our experience with 200 consecutive simultaneous pancreas-kidney (SPK) transplantations during a 7-year period.*

Methods. *Two hundred consecutive SPK transplantations were performed between December 1985 to October 1992. Immediate posttransplant function and surgical and infectious complications were evaluated. Frequency of rejection episodes were analyzed, as was 5-year patient and graft survival.*

Results. *All but four pancreas transplants functioned immediately after transplantation. Three pancreas transplants failed because of thrombosis and one from primary nonfunction. Five-year patient survival was 90.2%, kidney survival 80.3%, and pancreas survival 78.6%. There were 54 surgical complications. Fifteen patients have died since 1985. The most frequent cause of death was infection (three patients). A total of 678 infectious episodes were recorded. Urinary tract infection ($n = 344$) was the most frequent type of infection. Enteric conversion was necessary in 35 patients, with the most frequent indication being a leak of the duodenal segment.*

Conclusions. *We concluded from this series that SPK transplantation is associated with higher cost and morbidity as* *compared with kidney transplantation alone. However, excellent long-term survival in combination with the clearly demonstrated benefits for secondary diabetic complications indicate that SPK transplantation is the procedure of choice for carefully selected patients with diabetes. (*SURGERY *1993;114:736-44.)*

Endorectal advancement flap repair of rectovaginal and other complicated anorectal fistulas

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Background. *Surgical correction of rectovaginal and complicated anal-perineal fistulas has been associated with high rates of complications and failure of repair.*

Methods. *This paper reports on 107 patients treated during the past 10 years by endorectal advancement flap repair. Ninety-two percent of the patients were women with mean age of 38 years (range, 20 to 71 years). Seventy-one had low rectovaginal, 28 had anterior anal-perineal, and 8 had posterior anal-perineal fistulas. The causes were obstetric injury, 48; cryptoglandular abscess-fistula, 31; Crohn's disease, 24; and trauma or after operation, 4. The technique completely preserves the sphincter muscle, covers the internal opening of the fistula tract with healthy rectal wall, and provides counter drainage to aid healing.*

Results. *No deaths occurred in the series. Persistent or recurrent fistula occurred in 17 patients (16%). Nine patients whose initial operation failed underwent a secondary successful operation. Continence status was unchanged in 80%, improved in 18%, and was unknown in two patients who still had intestinal flow diversion. Recurrence of the fistula did not result in destruction of the sphincter mechanism in those patients who underwent simultaneous reconstructive operation.*

Conclusions. *The endorectal advancement flap repair successfully treated 93% of the complicated anorectal fistulas, avoiding fecal diversion and improving, not injuring, sphincter function. (*SURGERY *1993;114:682-90.)*

Determination of malignancy of thyroid nodules with positron emission tomography

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Background. *Current noninvasive evaluation techniques of thyroid nodules are nonspecific. We studied the use of a new noninvasive imaging modality, positron emission tomography (PET), in the evaluation of thyroid nodules.*

Methods. *Nineteen patients were studied before operation with PET with [^{18}F]-2-deoxy-2-fluoro-D-glucose (FDG). Twelve patients had solitary thyroid nodules and seven had multinodular goiters. Fourteen overlapping transverse slices were acquired through the thyroid gland. A region of interest was drawn around the abnormal area and the maximum pixel value was calculated and corrected to produce a normalized value for FDG uptake.*

Results. *Four of the 12 nodules were malignant (three papillary and one follicular carcinoma), with the others being follicular adenomas. All of the multinodular goiters were benign. All of the malignancies had an FDG greater than 8.5 and all of the benign nodules had an FDG less than 7.6. The dose uptake ratio of FDG was 10.8 ± 3.2 (mean ± SD) for the malignancies and was significantly greater than the dose uptake ratio of either the follicular adenomas (4.3 ± 2.0) or the dominant nodule in multinodular goiters (3.0 ± 2.0).*

Conclusions. *The FDG uptake as measured by PET scanning successfully discriminated between all benign and malignant tumors. This technique appears useful in the evaluation of thyroid nodules. (*SURGERY *1993;114:728-35.)*

Transjugular intrahepatic portosystemic shunt in the management of variceal bleeding: Indications and clinical results

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Background. *Transjugular intrahepatic portosystemic shunt (TIPS) has proved to be a successful bridge to liver transplantation in the management of variceal bleeding. The safety and ease of this technique has now challenged standard surgical approaches to portal hypertension. To define the role of TIPS, we prospectively studied patients undergoing this procedure for variceal bleeding and/or ascites.*

Methods. *From September 1991 to September 1992, 45 patients entered a protocol that included assessment of liver chemistries, ammonia levels, coagulation profiles, liver synthetic function by caffeine-antipyrine clearance, ultrasonographic evaluation of hepatic and portal veins, portogram and direct measurement of portal vein pressures, upper endoscopy, computed tomography for liver volume and ascites, and formal neuropsychiatric evaluation. These studies were repeated at 3-month intervals or more frequently if bleeding or complications occurred.*

Results. *Technical success and control of bleeding were achieved in all patients with only three (7%) variceal rebleeds from recurrent portal hypertension. Complete and permanent control of clinical ascites was noted in all patients with this complication. Five of six deaths occurred from sepsis and multiorgan failure in intensive care unit-bound patients with Child class C liver disease. No serial changes were noted in liver chemistries; however, progressive loss of liver volume and prolongation of caffeine-antipyrine clearance was observed in most patients. In addition, hepatic vein stricture or shunt stenosis seen in nine patients (20%) required TIPS revision, whereas the frequent appearance of symptomatic encephalopathy was a main indication for transplantation in 11 of 14 patients.*

Conclusions. *TIPS successfully controls variceal bleeding and may serve as a novel approach to control of diuretic resistant ascites. The uncertain long-term patency and progressive decline in synthetic function emphasize the importance of initiating proper trials comparing TIPS with other management strategies before indiscriminate use of this technique is seen. (*SURGERY *1993;114:719-27.)*

Correspondence

Herniation at the site of cannula insertion after laparoscopic cholecystectomy

Letter 1

Sir

I read with interest the Case Report by Messrs McMillan and Watt (*Br J Surg* 1993; **80**: 915) concerning the herniation of small intestine through the site of insertion of a 10-mm cannula after laparoscopic cholecystectomy. Unfortunately this is not the first report of this acute complication, which has been recorded at least twice previously[1,2]. There have also been letters published casting doubt on their conclusion that fascial closure of the unextended 10-mm defect is required to prevent this occurrence[3,4].

All three of these patients were symptomatic within 3 days, and I have not yet seen a report of a similar herniation of small intestine at a later stage after laparoscopic operation. Thus it appears that the cause of herniation is likely to be perioperative and, as I have written previously[3], probably related to the method of cannula removal.

Messrs McMillan and Watt state that they expelled all the carbon dioxide before extraction of the subumbilical cannula, a practice that is normal at present in laparoscopic cholecystectomy. However, when this manoeuvre is performed there is a pressure gradient between the gas in the peritoneal cavity and the atmosphere, allowing small bowel or omentum to become attached to the end of the cannula and then held there by the pressure differential. The act of withdrawing the cannula will pull the attached bowel into the wound and cause the hernia.

In addition, the defect in the anterior abdominal wall fascia is produced by the dilating effect of the 10-mm trocar and this is then held open by the cannula. The removal of this cannula allows the defect to close suddenly, reducing the size of this small hole and causing it to act as a sphincter, holding any misplaced bowel within the wound. Obviously, if bowel or omentum is pulled far enough through the abdominal wall it will be seen and replaced immediately. It is when the viscus is trapped only within the deeper layers of fascia, where it cannot be seen, that the danger arises. Therefore in laparoscopic trocar wounds up to 10 mm that have not been extended, I suggest that careful digital examination of all the cannulation sites at the end of the operation is more likely to avoid this complication than attempted fascial repair of these very small defects.

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Letter 2

Sir

We were interested to read the Case Report by Messrs McMillan and Watt regarding herniation at the site of cannula insertion after laparoscopic cholecystectomy (*Br J Surg* 1993; **80**: 915). We would like to communicate our own experience regarding this complication.

Of 780 patients operated on by a laparoscopic approach in our service, four developed herniation at the insertion site. Two patients who had undergone colorectal surgery presented with evisceration of the greater omentum. A cannula of 12 mm diameter had been used, and the insertion site was not extended. On the third day after operation they developed a painful small swelling deep to the insertion site. The wound was explored under local anaesthesia. The eviscerated omentum was reduced and the fascial defect was closed. The other two patients presented with small bowel herniation at the site where 10- and 12-mm cannulas had been inserted. They developed evidence of small bowel obstruction on day 4 after operation. Reoperation was carried out the same day, and intestinal resection was not necessary.

We believe that a careful exploration and closure of all 10- and 12-mm wounds is necessary, especially those situated in the infraumbilical region.

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Letter 3

Sir

We read with interest the article by Messrs McMillan and Watt (*Br J Surg* 1993; **80**: 915). We have also had one case of uncomplicated herniation at the umbilical incision requiring repair. Thus, we have adopted a technique to lessen the risk of bowel herniation through the laparoscopic port incisions and reduce the risk of accidental injury to abdominal structures from the needle or trocar. We use a 'cut down' technique to the peritoneum and then place a no. 2 polyglactin purse string in the linea alba. After insertion of a reusable 10-mm cannula, the purse string is tightened and secured with one throw of a knot; the knot is held with an artery clip. At the end of the procedure, the pneumoperitoneum is deflated through the 10-mm cannula before its removal. The purse string is then tightened, and secured with two further knots.

The technique is slightly slower than using a Veress needle to establish pneumoperitoneum, but it has the advantage of placing the cannula under direct vision and providing secure closure. The latter is faster than repairing the fascial defect with a suture once the cannula is removed. Leakage of carbon dioxide around the purse string is minimal and if present can be reduced by placing a swab into the skin wound.

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Letter 4

Sir

The recent interesting paper by Messrs McMillan and Watt (*Br J Surg* 1993; **80**: 915) prompts us to report a similar complication. A 74-year-old woman underwent an uncomplicated laparoscopic cholecystectomy but complained of abdominal pain and vomiting on the second day after operation. This settled with conservative treatment but on day 6 she developed small bowel obstruction and a swelling was noted beneath the subumbilical skin incision. This was explored and an obstructed loop of small bowel, surrounded by a small collar of peritoneum, was found. The subsequent recovery was uneventful.

We believe that a small umbilical hernia existed before operation and that the 10-mm port passed through it, facilitating herniation of the small bowel through the sac and into the subcutaneous tissue. We now close all fascial defects at 10-mm ports.

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The article by Messrs McMillan and Watt generated much correspondence, with nine previously unreported instances of this complication coming to light. The matter is now, however, closed.

Editor

Laparoscopic cholecystectomy

Sir

We read with interest the Review on laparoscopic cholecystectomy by Messrs Macintyre and Wilson (*Br J Surg* 1993; **80**: 552–9). The authors state that one of the generally agreed contraindications to laparoscopic cholecystectomy is the presence of a cholecystoenteric fistula.

We have encountered five cholecystoduodenal fistulas in a series of 300 laparoscopic cholecystectomies, which we are reporting in *Surgical Laparoscopy and Endoscopy*. Of these, two were diagnosed before operation. One patient had a previous cholecystoduodenostomy and another had aerobilia on computed tomography. It was possible to deal with four fistulas laparoscopically. The fifth patient had to undergo conversion to laparotomy as the duodenum was inadvertently perforated during dissection. In the remainder it was possible to display the cholecystoduodenal fistula with a combination of careful blunt and sharp dissection. The fistula was divided and stapled at the same time by a single firing of an Endo-GIA30 stapler (US Surgical, Norwalk, Connecticut, USA) through an epigastric 12-mm cannula. Intraoperative cholangiography was performed in each patient to confirm biliary anatomy and detect bile duct stones.

We maintain that, with increasing expertise, better imaging and improved instrumentation, it is feasible to repair most cholecystoduodenal fistulas laparoscopically.

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New adjustable knot for securing subcuticular running sutures

Sir

We read with interest the Surgical Workshop by Dr Di Saverio and colleagues on an adjustable knot for securing subcuticular sutures (*Br J Surg* 1993; **80**: 873). Careful adjustment of tension and a small knot might well reduce the problems associated with anchoring subcuticular sutures to the skin surface. However, where an absorbable suture is used, the marked skin and potential route of infection from the skin surface can be avoided by other techniques.

Ranabaldo[1] recently described a knotless technique involving several acutely angled passages through the subcutaneous tissue. Occasional immediate gaping was admitted, suggesting that the technique may be less suitable for low-friction monofilament sutures.

We believe that the problems of knot ulceration with absorbable subcuticular suturing can be avoided by using very light gauge material. Since 1992, one general surgeon (F.L.H.) has used 5/0 polydioxanone for all incisions except some on the face and scrotum. A three-throw conventional buried knot is used proximally and a three-throw Aberdeen knot distally. The cases include a large number of mastectomies and other breast procedures, laparotomy wounds and lower-limb amputations. The suture is also used by junior surgeons with no previous experience in subcuticular closure with such a small needle and fine material. Over 500 closures have been performed with no early wound dehiscence. Most major incisions have been reviewed in outpatients for other reasons, and no knot protrusion has been detected. The few wounds known to have dehisced were associated with infection among patients in whom a high incidence of wound problems might have been expected. Dehiscence occurred in a small part of a midline incision after proctectomy for Crohn's disease in an octogenarian with a low albumin level and recent steroid medication.

This suture dictates a meticulous technique, distributing tension over multiple small bites, and this contributes to a good cosmetic result.

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Return to work after inguinal hernia repair

Sir

I read with interest the Short Note by Dr Rider and colleagues (*Br J Surg* 1993; **80**: 745–6). I was surprised at the decision to study this subject retrospectively over a 10-year period. Patient recall of subjective matters such as preoperative expectations of convalescence are strongly susceptible to bias at the best of times and cannot safely be analysed in retrospect, especially when the events being recalled may have occurred many years before. More objective data such as the length of time off work would still be difficult to evaluate unless corroborated by means of an independent source such as employment records or general practitioner's notes, and I can find no reference to this sort of information in the study. In the light of these methodological difficulties, which are to some extent inherent in retrospective analysis but accentuated in this study, I did not feel it is justifiable to draw the conclusion that the time off work following routine inguinal herniorrhaphy is reducing.

In a prospective study I conducted 2 years ago, for 101 patients from the Northern health region, the median time off work following inguinal hernia repair was 45 (interquartile range 23–83) days. This was of similar length to the figures quoted from earlier studies. Although there was a greater proportion of patients performing heavy work (37 *versus* 27 per cent), the same relationship between type of work and time off was not observed. Perhaps more significant was the observation that only 20 per cent of patients received advice concerning return to work before operation and 44 per cent after surgery. Some 63 per cent of patients made their own decision about when to return to work without consulting either their general practitioner (GP) or surgeon.

I agree with the authors that there is a great need for better preoperative education of patients (in particular) and GPs concerning the appropriate time of return to work, but I do not feel that they have presented adequate evidence to suggest that the current position is improving.

S. E. Stock

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Authors' reply

Sir

We feel the strength of our study lies in considering inguinal hernia operations performed by only one surgeon, but we accept the shortcomings of its retrospective nature. Considering procedures performed by only one surgeon removes the influences on return to work of both variable hospital doctor advice (which does occur[1]) and differences in operation technique.

In Nottingham, time off work following routine inguinal herniorrhaphy appears to be reducing. In 1978 a mean of 78 (range 18–229) days convalescence was taken[2]. By 1991 this figure had fallen[2] to 28 (range 0–120) days. As previously suggested[1], it is possible that patients in Nottingham return to work today earlier than elsewhere.

Mr Stock's findings suggest that in the Northern health region, unlike elsewhere[1,3], views on when to return to work are correctly independent of the physical content of the patient's job.

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1. Baker DM, Rider MA, Locker A, Fawcett AN. How long do patients convalesce after inguinal herniorrhaphy? *Ann R Coll Surg Engl* 1993; **75**: 216 (Comment).
2. Bourke JB, Taylor M. The clinical and economic effects of early return to work after elective inguinal hernia repair. *Br J Surg* 1978; **65**: 728–31.
3. Robertson GS, Haynes IG, Burton PG. How long do patients convalesce after inguinal herniorrhaphy? Current principles and practices. *Ann R Coll Surg Engl* 1993; **75**: 30–3.

Randomized study of the value of laparoscopy before appendicectomy

Sir

I read with interest the article by Dr Olsen and colleagues on the value of laparoscopy before appendicectomy in women (*Br J Surg* 1993; **80**: 922–3). The use of laparoscopy in the diagnosis and treatment of acute appendicitis is becoming widespread in this country and elsewhere in the world. Although this technique is very useful in confirming acute appendicitis and also in diagnosing other pathologies (especially gynaecological ones), practising surgeons must be wary of the 'laparoscopically normal' appendix.

Dr Olsen and colleagues used the criterion that appendicitis could be excluded 'if a normal appendix could be seen throughout its length'. However, a recent study by Grunewald and Keating[1] showed that, at open operation, surgeons diagnosed a normal appendix incorrectly in 26 per cent of patients when it was subsequently checked histologically. Furthermore, when the appendix appeared normal and no other pathology could be found, the false-reassurance rate rose to 29 per cent.

The laparoscope affords excellent views of much of the peritoneal cavity and allows visualization of the pelvic organs while causing minimal morbidity to the patient. It also magnifies the appendix, allowing very close inspection of this structure. Unfortunately, there are no data to show conclusively that laparoscopic assessment of the 'normal' appendix is any more accurate than inspection at open operation. My own attempts at assessing the turgidity of the 'normal' looking appendix via the laparoscope (the 'wobbly' sign) and comparing this with subsequent histological findings in an attempt to identify the hidden inflammation has shown no correlation.

Therefore, in the face of such a high false-reassurance rate it is inadvisable at present to leave a laparoscopically normal appendix, especially if the clinical picture is suspicious of appendicitis and no other cause of pain can be identified.

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1. Grunewald B, Keating J. Should the 'normal' appendix be removed at operation for appendicitis? *J R Coll Surg Edinb* 1993; **38**: 158–60.

Detection and enumeration of circulating tumour cells in colorectal cancer

Sir

We read the article by Mr Leather and colleagues (*Br J Surg* 1993; **80**: 777–80) with great interest as we are conducting a similar study in patients with breast cancer. We have several comments to make.

First, the assumption made by the authors that tumour and mononuclear cells are deposited with equal efficiency at the interface following density-gradient centrifugation is probably incorrect. Previous work[1] has shown that the specific gravity of tumour cells ranges from 1·040 to 1·070 whereas that of mononuclear cells is between 1·060 and 1·075. The efficiency of cell recovery is therefore likely to be higher for mononuclear than tumour cells when Histopaque (Sigma Chemicals, Poole, UK; specific gravity 1·077) is used. Second, we are surprised to see that the authors detected as few as 10 tumour cells/ml in three of five attempts and achieved such a high rate of tumour cell recovery. Glaves[2] has reported an efficiency of tumour cell recovery as low as 16 per cent using a similar method with Percoll (Sigma Chemicals). Our own experience suggests a value that may be even lower. We used a similar method with Ficoll–Hypaque (Sterling Winthrop, Guildford, UK; specific gravity 1·077) and calculated the percentage of tumour cell recovery after adding a known number of tumour cells to blood from healthy volunteers. After the experiments were repeated 15 times, the mean tumour cell recovery was only 4 per cent. We are also interested to know the methodology used by the authors to count the relative number of tumour cells to mononuclear cells on cytospins. Sampling error can easily occur if the density of mononuclear cells varies between cytospins and between different areas on the same cytospin.

This is an important but difficult field of work, with major potential implications for clinical practice. This fact makes it all the more important that the methods used to study circulating tumour cells are extremely robust.

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1. Fleming JA, Stewart JW. A critical and comparative study of methods of isolating tumour cells from the blood. *J Clin Pathol* 1967; **20**: 145–51.
2. Glaves D. Correlation between circulating cancer cells and incidence of metastases. *Br J Cancer* 1983; **48**: 665–73.

Vein-patch rupture after carotid endarterectomy: an avoidable catastrophe

Sir

We read with interest the article For Debate by Mr John and colleagues (*Br J Surg* 1993; **80**: 852–3) and agree with many of the points made within it. It has been our policy to use upper-thigh saphenous vein since 1990, when two cases of vein-patch rupture occurred after the use of lower-leg vein. A review of the literature convinced us of the advantages of upper-thigh vein and, until very recently, over 170 carotid endarterectomies had been performed with no recurrence of the problem.

However, we have now experienced our first case of upper-thigh saphenous vein-patch rupture following carotid endarterectomy. The patient, a 51-year-old man, presented with a history of recurrent transient ischaemic events in the left carotid territory. Carotid duplex scanning revealed 75 per cent stenosis of the left carotid artery and an occluded right carotid artery, on which endarterectomy had been performed 8 years previously. During the intervening period the patient had also undergone coronary artery bypass grafting, which had utilized all the long saphenous vein from the right leg. At operation the saphenous vein harvested from the left thigh was of small calibre for a man but considered acceptable for patching. A 30-min period of postoperative hypertension was controlled with intravenous labetalol infusion, and for the first 3 days the patient made a good recovery. On day 4 the vein patch ruptured; at operation it was found to have split down the middle in the characteristic axial direction[1].

This case underlines the importance of the diameter of the saphenous vein in patch rupture[1]. In patients whose saphenous vein is unsuitable to patch the carotid artery, several alternatives are available, although complications have been associated with all of them. Jugular vein is tempting because of its location, but the tensile strength of internal and external jugular vein is one-quarter that of large saphenous vein, and external jugular vein in particular has a very low rupture pressure[1]. Polytetrafluoroethylene (PTFE) patches can be used, but PTFE patch disruption has been reported[2] and cases of delayed postoperative bleeding from stitch holes have also occurred[3]. Woven Dacron (Du Pont, Stevenage, UK) is a useful alternative, but care must be taken to use material specified for the purpose as other forms of Dacron carry the risk of fraying. As with all artificial materials there is the risk of infection; we recently experienced a case of chronic carotid endarterectomy wound infection that was cured only by replacing the artificial patch with vein. Other sources of patch material such as superior thyroid artery have failed to gain popularity.

Vein-patch angioplasty for carotid endarterectomy has been shown to reduce the risk of early postoperative carotid thrombosis, long-term restenosis and recurrence of symptoms[4]. By contrast, there is a risk of patch rupture, which is a rare but serious complication. We agree with John and colleagues that this complication can be minimized by using good-quality upper-thigh saphenous vein, giving particular attention to the diameter of the vein. Nevertheless, we believe that the incidence of vein-patch rupture can be reduced by these guidelines but the complication probably never completely avoided.

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1. Archie JP Jr, Green JJ. Saphenous vein rupture pressure, rupture stress, and carotid endarterectomy vein patch reconstruction. *Surgery* 1990; **107**: 389–96.
2. Rosenthal D, Archie JP, Gareia-Rinald R *et al.* Carotid patch angioplasty: immediate and long-term results. *J Vasc Surg* 1990; **12**: 326–33.
3. McCready RA, Siderys H, Pittman JN *et al.* Delayed post-operative bleeding from polytetrafluoroethylene carotid artery patches. *J Vasc Surg* 1992; **15**: 661–3.
4. Eikelboom BC, Ackerstaff RGA, Hoenveld H *et al.* Benefits of carotid patching: a randomized study. *J Vasc Surg* 1988; 7: 240–7.

'Car-crusher colon'

Letter 1

Sir

We read with interest the Case Report by Messrs Whiteley, Deardon and Pearson (*Br J Surg* 1993; **80**: 640). We recently treated a 40-year-old driver who was admitted to hospital after being injured by the jaws of a vehicle crane. An operating button had been pressed accidentally, and the patient's abdomen had been caught by the jaws of the crane. On examination he had left-sided abdominal pain and haemoperitoneum. Laparotomy revealed a ruptured spleen and a 'degloving' injury of the sigmoid colon. Around 6 cm of colon displayed an intact tube of mucosa. the injury to the mesentery was trivial; splenectomy and seromuscular repair of the sigmoid colon were performed. The patient made an uneventful recovery. Degloving injury of the bowel may not be rare and should be looked out for in patients with blunt abdominal injury.

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Letter 2

Sir

I was interested by the report of Messrs Whiteley, Deardon and Pearson (*Br J Surg* 1993; **80**: 640) on a degloving injury to the colon. The authors stated:

> 'Degloving of the skin from limbs is familiar following shear forces but to our knowledge no such degloving event has been reported in the layers of the large bowel, although the mode of injury is certainly by "shear"'.

This type of injury, termed 'degloving', was reported by me[1,2] as early as 1981. I do not claim originality; I am certain that it would have been reported previous to my use of the term although, like the authors, I was unable to find the appropriate documentation.

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1. Strong RW. Colorectal injuries. *Aust N Z J Surg* 1981; **51**: 285–8.
2. Strong RW. Blunt injuries of the large bowel. In: Fielding LP, Todd IP, eds. *Rob and Smith's Operative Surgery. Colon, Rectum and Anus.* 4th ed. London: Butterworths, 1983: 193–8.

Errata

The September issue and its Supplement contained the following errors.

1. Hatzitheofilou C, Strahlendorf C, Kakoyiannis S, Charalambides D, Demetriades D. Penetrating external injuries of the oesophagus and pharynx. *Br J Surg* 1993; **80**: 1147–9.

The number of patients given in line 2 of the abstract as 18 588 is incorrect. The correct value is 10 143.

2. Millat B, Fingerhut A, Gignoux M, Hay J-M, French Associations for Surgical Research. Factors associated with early discharge after inguinal hernia repair in 500 consecutive patients. *Br J Surg* 1993; **80**: 1158–60.

The number of patients unsuitable for short-stay surgery given as 59 in line 3 of the abstract is incorrect. The correct value is 89.

In one case a mistake was made by the author in amending the proof; in the other the mistake was present in the original manuscript. Authors are urged to exercise extreme care with data both in the preparation of manuscripts and in the correction of proofs.

3. Stanek A, Orzelski J, Wajda Z, Gruca Z, Marczewski R. Laparoscopic cholecystectomy: early results and experience. *Br J Surg* 1993; **80**: S48.

The authors' names were inadvertently left out from the above abstract presented at the recent Eurosurgery 93 meeting. The Journal apologizes to the authors for this omission.

Book reviews

Reconstructive Urology. Vols 1 and 2

G. Webster, L. King and B. Goldwasser (eds). 285 × 215 mm. Pp. 500 and 565. Illustrated. 1993. Oxford: Blackwell Scientific. £175.

Reconstructive Urology deserves to become the definitive text in this expanding area of surgery. In recent years there have been tremendous advances in this field and many of the leaders have contributed to these volumes.

Half of Volume 1 is devoted to the principles of reconstruction, reviewing physiology, anatomy, assessment and surgical techniques. Much of this is available in other books but its inclusion in this work is appropriate since there will be many occasions when the reader will wish to be reminded of basic principles. The book is well illustrated and produced in clear double-column text that makes for easy reading. It is comprehensive but there appears to be a blurring between conservation and reconstruction. While there clearly is an overlap in the management of urinary tract disorders, I found chapters on such topics as malignant kidney disease, retroperitoneal fibrosis and endoscopic management of ureteropelvic junction obstruction a little out of place. In this respect, Volume 2 is far more convincing and this is where the dedicated reconstructive surgeons will find much to interest them.

In the 1990s, for such a text to be economically viable it must serve an international market; this is the one area that I found irritating for it appears that good English words have been Americanized in an attempt to broaden the book's appeal. This makes part of the text appear stilted. I doubt, for example, that a British urologist really uses terms such as 'theoretic reason' and 'anatomic result'. However, these criticisms are minor and should not detract from what is a superbly produced book that deserves to become the reconstructive urologist's bible.

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Transurethral Resection. 3rd ed.

J. Blandy and R. Notley. 250 × 190 mm. Pp. 169. Illustrated. 1993. Oxford: Butterworth–Heinemann. £39·50.

The third edition of this well written book has been updated to include more details of closed-circuit television for the urologist, new information on the transurethral resection (TUR) syndrome and comments on the medical and surgical alternatives to TUR of the prostate that are in fashion. The outline of the book is unaltered. There is an interesting historical introduction, followed by a review of the basic physics of the technologies enabling the urological surgeon to perform TUR. The armamentarium is described, and the indications and investigations are discussed. The greatest strength of this book, however, remains its detailed description of technique. Although the teaching of TUR is now much easier with the introduction of closed-circuit television, the surgeon in training nevertheless must still have a thorough grasp of the surgical principles and basic technical steps. Nowhere are these more thoroughly described or more beautifully illustrated (the black and white illustrations are much more informative than the colour plates). Readers can enjoy the prose, which makes for easy and pleasurable reading. Postoperative care, and the prevention and management of complications are covered comprehensively. In a book of this size it is not surprising that there is no room to include comments on prostatic screening, transrectal ultrasonography and prostate-specific antigen. These controversial topics may be included in a fourth edition which will undoubtedly be required in due course, since this book is destined both to remain essential reading for every urologist in training, and to maintain its place on the bookshelves of every urology department.

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Minimally Invasive Surgery

J. Hunter and J. Sackier (eds). 285 × 220 mm. Pp. 358. Illustrated. 1993. Maidenhead: McGraw–Hill. £71·50.

If predictions that 70 per cent of all surgical operations will be performed by minimally invasive techniques by the turn of the century come true, this will be a very important book for surgeons. The editors – both pioneers in the field – work in the United States but acknowledge their British training and influence. It is disappointing therefore to see that only one contributor (Professor Cuschieri) comes from the UK, compared with seven from France and 36 from the States, reflecting perhaps the relative contributions that each of these countries has made to the new technology.

Early chapters are appropriately devoted to the new technologies that have made the surgical revolution possible. Consecutive chapters deal with fibreoptics, ultrasound, lasers, electrosurgery and surgical polymers. The bulk of the book is devoted to the description of individual techniques; due prominence is given to laparoscopic suturing and anastomosis. The layout of the book is pleasing, with double columns and effective use of subheadings. The quality of the illustrations is high and the line drawings of operative procedures in particular are models of clarity. Minimally invasive procedures within the abdomen and pelvis are comprehensively covered along with a short chapter on thoracoscopic surgery. In addition, endoluminal endoscopic techniques of the gastrointestinal tract merit chapters in their own right, as does endovascular surgery.

This is a clear, comprehensive, well illustrated and well referenced textbook. For this reviewer it is the best so far produced in the field and is highly recommended.

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Surgical Decision Making. 3rd ed.

L. W. Norton, G. Steele Jr and B. Eiseman (eds). 220 × 280 mm. Pp. 342. Not illustrated. 1993. Philadelphia, Pennsylvania: W. B. Saunders. £55.

This is an excellent book. Assimilation of complex methods of treatment in general surgery is becoming increasingly difficult, particularly as specialization continues a pace. The essential form of this book is to keep each chapter to two pages facing one another. The basis of each chapter is an algorithm beginning with history, examination and investigations, and extending – depending on the findings – into the various management options. The algorithms are always on the right-hand page and at major decision points there are keys enabling the reader to refer to items of text on the left-hand page. Each chapter also contains a handful of good up-to-date references. The whole book works extremely well, partly because the editors have exploited a large number of specialists to deal with each of the sections. In all there are 334 chapters divided into 11 sections: general, head and neck, cardiopulmonary, gastrointestinal, breast and soft tissues, vascular, paediatric, transplantation, urological, gynaecological and orthopaedic. The book is well indexed.

I found this volume easy to use and the algorithms were thoughtful, up to date and well laid out. Inevitably, there will be aspects with which not every reader will agree, but in principal there was little I could find to fault. This book will be extremely useful for those undertaking specialist examinations and those involved in undergraduate and postgraduate teaching. It may also be helpful for the busy clinician. The success of such a book demands that it remain up to date, incorporating new data as they arrive; I am not surprised that it is in its third edition. This volume should be found in every postgraduate medical library – it is a pity that it is not available in paperback.

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Atlas of Surgical Pathology

J. Turk and C. Fletcher. 315 × 255 mm. Pp. 346. Illustrated. 1992. London: Gower Medical. £99.

In 1985 Gower Medical commissioned a slide atlas comprising eight volumes of colour transparencies of the magnificent collection of pathological specimens in the museum of The Royal College of Surgeons of England, which dates back to 1799 when parliament bought John Hunter's collection. Each eight-volume set cost over £1000 but they sold quite well to medical schools that had not yet built up their own pathology museums. Over 1000 of these photographs have now been published in full colour, together with their accompanying text.

Many of the more bizarre congenital malformations, which have little educational value, have been omitted, but there are few surgically important lesions – adult respiratory distress syndrome is one – that are not represented. From time to time I wished that the photograph of the gross specimen had been accompanied by a photomicrograph, but no doubt that would have doubled the price.

This is not a 'coffee table' book, but a serious volume of surgical pathology. I am not sure which to admire most, the skill of the photographer or the erudition of the text writer. Each photograph is accompanied by a description of the specimen, its provenance and clinical history (if they are known), and a teaching paragraph that is quite enough to satisfy the requirements of the examiners for Fellowship of any of the Royal Colleges. Despite this, I am not sure for whom the book is intended; at £99 it is beyond the means of most Fellowship candidates. Nevertheless, it is a superb book that is worth saving up for, and it will not go out of date.

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Atlas of Vascular Surgery – Basic Techniques and Exposures

R. Rutherford. 285 × 220 mm. Pp. 267. Illustrated. 1993. Philadelphia, Pennsylvania: W. B. Saunders. £57.

In the preface the author confesses to a longstanding disappointment with surgical atlases, largely because they focus on the final stages without demonstrating the essential intermediate steps. To counteract this Dr Rutherford has written an atlas of vascular surgery and divided it into two sections, the first of which deals with basic vascular technique and the second with vascular exposure. In the first section the historical background is described along with instruments and suture material. The section then goes on to discuss vascular exposure and control, haemostasis and anticoagulation, vascular incisions, closures and anastomoses. The remainder of this section deals with preparation of grafts, tunnelling, thromboembolectomy, endarterectomy and perioperative arteriography. The illustrations are beautifully drawn and well annotated; the descriptive narrative is clear and concise. This section is aimed as an introduction to basic techniques and clearly accomplishes its task. The second section deals with vascular exposure and is once again well illustrated with clear and simple diagrams. In particular the approach to the suprarenal aorta is lucidly described. There is also an interesting section on the lateral approach to the popliteal artery that is seldom used in this country. At £57 this book represents excellent value, not only for beginners in vascular surgery but also for those actively engaged in its practice. It also complements admirably Rutherford's *Text Book on Vascular Surgery*.

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Surgery for All. A View from the Developing World

M. Ahmed, R. J. W. Blanchard, B. Eklof, T. S. Harrison, F. Moazam, S. K. Suleman, J. Talati and S. Tibblin. 250 × 190 mm. Pp. 419. Illustrated. 1992. Lahore: Arkash Publishing. £15.

This is a difficult book to review and I am left in some doubt as to the target readership the multiple authors had in mind when assembling the chapters. The foreword does little to clarify the situation as it consists largely of a series of quotes from the text. The chapters cover both general surgical and specialty topics in the context of the country of origin of the author. It was interesting to be reminded of some of the infective agents causing general surgical problems in the Third World, but the specialty chapters are not detailed enough to form a useful reference text or instructive enough for a practical manual.

I did enjoy (and indeed could relate better to) the more general chapters. Particularly informative were those on prioritizing surgical care in Africa and surgery for the effects of chronic violence, which describes the evolution of the acute surgical services at the American University Hospital in Beirut as the Lebanon conflict escalated.

Peruse this book if you want to familiarize yourself with some of the acute surgical problems of the developing world. The colour photographs are of reasonable quality and enhance the text, although you may well be frustrated by the not so infrequent patches of poor English. However, I cannot recommend you to buy a copy for your personal library, although it is reasonably priced for a hardback volume.

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Notices and announcements

3 December 1993
Role of the Plain Abdominal Radiograph in the Acute Abdomen
Canterbury, UK
Information: Postgraduate Administrator, Kent Postgraduate Medical Centre, Kent and Canterbury Hospital, Canterbury CT1 3NG, UK

16–17 December 1993
Update in Digestive Oncology
Amsterdam, The Netherlands
Information: Managing Director, European Postgraduate Gastro-Surgical School, Academic Medical Centre, Meibergdreef 9, 1105-AZ Amsterdam, The Netherlands

6–7 January 1994
Surgical Research Society Meeting
London, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

15–16 January 1994
Hong Kong Surgical Forum – Winter 1994
Hong Kong
Information: Jane Yang, Forum Secretary, Hong Kong Surgical Forum, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong

19–22 January 1994
The California Trauma Conference
San Francisco, California, USA
Information: School of Medicine, Office of Continuing Medical Education, University of California, San Francisco, California 94 143-0742, USA

21–26 January 1994
Introduction to Molecular and Cellular Research
Orlando, Florida, USA
Information: The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20 814-3398, USA

23–28 January 1994
18th International Congress of Radiology
Singapore
Information: 18th ICR '94, Kent Ridge, PO Box 1052, Singapore 9111

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12 203 Berlin, Germany

9–13 February 1994
European Society of Anaesthesiologists
Brussels, Belgium
Information: Mrs Mary Roe, Options Eurocongress SA, Rue Washington 129, B-1050 Brussels, Belgium

14–18 February 1994
Controversies and Recent Advances in Surgical Pathology
San Diego, California, USA
Information: Armed Forces Institute of Pathology, Education Division, Washington, DC 20 306-6000, USA

17–18 February 1994
New Trends in the Diagnosis and Treatment of Oesophageal Cancer
Amsterdam, The Netherlands
Information: Managing Director, European Postgraduate Gastro-Surgical School, Academic Medical Centre, Meibergdreef 9, 1105-AZ Amsterdam, The Netherlands

21–23 February 1994
Seventh Annual Congress of the North American Society of Phlebology on the Advances in Medical and Surgical Treatment of Venous Disorders
Wilea, Hawaii, USA
Information: North American Society of Phlebology, 523 Encinitas Boulevard, Suite 108, Encinitas, California 92 024, USA

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

28–29 March 1994
Injury Research Group Meeting
Swindon, UK
Information: Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, Oxford Road, Manchester M13 9PT, UK

11–13 April 1994
Third International Symposium on Budd–Chiari Syndrome
London, UK
Information: Professor K. E. F. Hobbs, University Department of Surgery, Royal Free Hospital, Pond Street, London NW3 2QG, UK

16–19 April 1994
SAGES 1994 Scientific Session and Postgraduate Course – Complications of Laparoscopy and Flexible Endoscopy
Nashville, Tennessee, USA
Information: Society of American Gastrointestinal Endoscopic Surgeons, 117 01 Texas Avenue, Suite 101, Los Angeles, California 90 025, USA

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20040-030 Rio de Janeiro, Brazil

26–28 May 1994
Surgical Infection Society of Europe 7th Annual Meeting
Vienna, Austria
Information: Professor F. Schulz, c/o Wiener Medizinische Akademie für Ärztliche Fortbildung, Alser Straße 4, A-1090 Vienna, Austria

2–6 July 1994
XVth Biennial Congress of the International Society of University Colon and Rectal Surgeons
Singapore
Information: ISUCRS XVth Congress Secretariat, c/o Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 0316

7–8 July 1994
Surgical Research Society Meeting
Glasgow, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1994
VIIIth Edmondo Malan International Surgery Days – Difficult Surgical Problems
Parma and Colorno, Italy
Information: Professor G. C. Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43 100 Parma, Italy

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW, Suite 300, Washington, DC 20005, USA

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to: The Senior Editor, *The British Journal of Surgery*, Blackwell Scientific Publications Ltd, 25 John Street, London WC1N 2BL, UK. Telephone: 071-404 1831. Facsimile: 071-404 1927.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

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These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 400 words (300 if accompanied by a figure), with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications*. New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

COMPLICATIONS OF LAPAROSCOPY AND HYSTEROSCOPY

Edited by R S Corfman, M Diamond and A DeCherney

086542201X, Hardback, £45.00, Jan-93,
288 pages, 86 illustrations

Many surgical procedures in gynaecology are now performed by means of endoscopy or 'keyhole surgery' rather than by traditional surgery, thereby reducing hospital stays and cutting costs. The number and difficulty of such procedures is growing constantly. This book deals with potential complications of such techniques and how to avoid and rectify them.

The contents deal with all the major procedures, including sections on: preoperative and postoperative considerations, anesthesiology, intraperitoneal insufflation and trocar placement, complications arising from vaginal placement of accessories, operative laparoscopy, specific gynecological procedures, hysteroscopy, general surgery and other surgical complications. Their complications are addressed in detail to help the practitioner better understand each procedure and its potential problems.

- covers all the major procedures;
- deals with increasingly popular and complicated techniques;
- enables the practitioner to operate more safely;
- responds to the growing trend towards day case surgery.

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sentation: Ampoule containing 5ml of
% aqueous solution of dopexamine
lrochloride (50 mg).
es: Short term intravenous administration
the treatment of heart failure associated with
diac surgery.
sage and Administration: Dopacard must
diluted before use and administered
ravenously via a cannula or catheter into a
ntral or large peripheral vein. A device which
vides accurate control of the rate of flow of
ision is essential.Full instructions are given in
data sheet and package insert.
paration: The contents of four ampoules
uld be injected aseptically into one of the
owing: 0.9% Sodium Chloride Injection or
Dextrose Injection (500 or 250ml).
commended dosage for adults including the
erly: Infusion should begin at a dose of 0.5
kg/min and may be increased to 1μg/kg/min
l then in increments (0.5-1 μg/kg/min) up to
g/kg/min at not less than 15 minute intervals,
ording to the patient's haemodynamic and
iical response. The rate of administration
l duration of therapy should be adjusted
ording to the patient's response as determined
heart rate and rhythm (ECG), blood pressure,
ne output and, whenever possible,
asurement of cardiac output. Extended
rapy beyond 48 hours has not been fully
iluated. It is recommended that the infusion
Dopacard is reduced gradually.
ntra-indications, Precautions, Warnings:
ntra-indications: Known hypersensitivity
dopexamine hydrochloride or excipients
sodium edetate). Concurrent MAOI
ninistration, left ventricular outlet obstruction
ch as hypertrophic obstructive
diomyopathy or aortic stenosis),
aeochromocytoma, thrombocytopenia.
cautions: If any correction of hypovolaemia
equired this should be achieved before the
ninistration of Dopacard.
rnings: Dopacard should be administered
h caution to patients with a clinical history
schaemic heart disease especially following
ite myocardial infarction or recent episodes of
gina pectoris. A small, reversible fall in
culating platelet numbers has been observed in
ne patients. No adverse experiences
ributable to alterations in platelet count have
en seen in clinical studies. Plasma potassium
y decrease and blood glucose may increase
ing Dopacard administration and care is
uired in its use in patients with, or at risk of,
pokalaemia or hyperglycaemia. In patients
h a marked reduced systemic vascular
istance, Dopacard should not be used as a
ect substitute for pressor agents or other
tropes. If cardiac arrhythmia should occur,
dosage should be reduced or infusion
continued. There have been occasional
orts of partial tolerance, with some
enuation of the haemodynamic response
eloping during long term infusions of
pacard. The safety and efficacy of Dopacard
use in children has not been established.
e in Pregnant and Lactating Women:
pacard is not currently recommended for use
pregnant and lactating women.
e effects: Dose-related increases in heart
e may occur during infusion of Dopacard; in
st cases these are not clinically significant.
casionally excessive tachycardia or ventricular
rasystoles, and, more rarely, atrial fibrillation,
ve been noted during the infusion,
cessitating reduction or temporary
continuation of the infusion. Tachycardia
y be more pronounced in patients with pre-
sting atrial fibrillation. The following side-
ects have been reported infrequently, in most
es at high dosage: Nausea, vomiting,
potension, dyspnoea, headache, hypertension,
mor, chest pain, cardiac failure, increased
eating, angina pectoris.
eractions: Dopacard may potentiate the
ects of exogenous noradrenaline and may
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pamine. Caution in the concomitant use of
- adrenergic and dopamine receptor
agonists because of possible attenuation of the
rmacological effects of Dopacard.
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l: (0628) 771417. **NHS Cost:** £18.94 per
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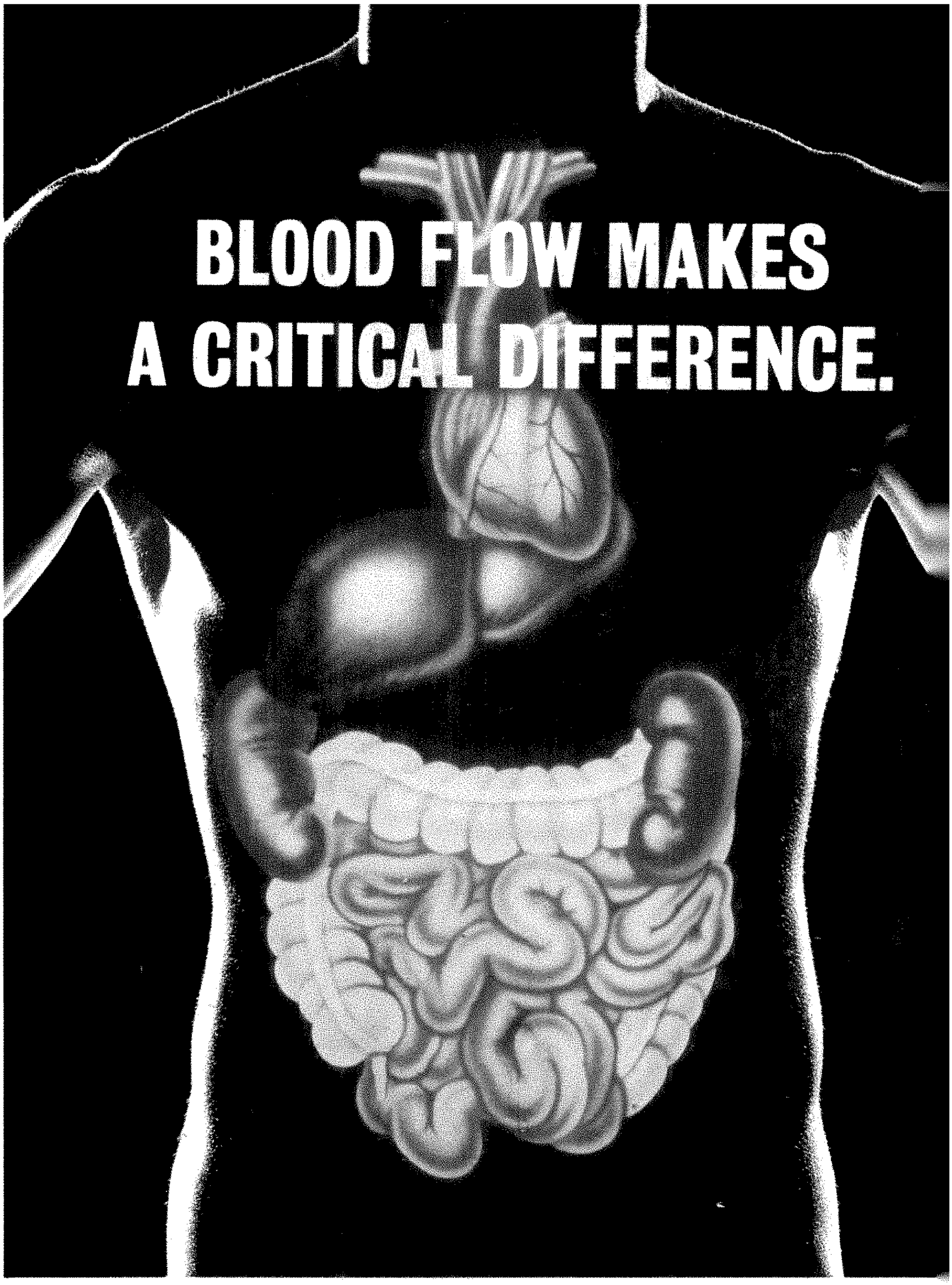

DOPACARD increases cardiac output and enhances both renal and mesente
blood flow. This combined activity makes it of value for patients with low ca
output associated with cardiac surgery.

DOPACARD achieves its effects by combining dopaminergic and β_2 adrenerg
agonist activities. Substantial cardiac output increases are frequently obtaine
mostly by afterload reduction, with no significant change in myocardial
oxygen consumption.

The distribution of the increased cardiac output to vascular beds such as the
kidney, liver and gut, without the risk of vasoconstriction, offers improved blc
flow to these vital organs.

DOPACARI
dopexamine hydrochlor

Increasing Renal and Hepato-Splanchnic blood flo

Prescribing information

Presentation: Ampoule containing 5ml of a 1% aqueous solution of dopexamine hydrochloride (50 mg).

Uses: Short term intravenous administration for the treatment of heart failure associated with cardiac surgery.

Dosage and Administration: Dopacard must be diluted before use and administered intravenously via a cannula or catheter into a central or large peripheral vein. A device which provides accurate control of the rate of flow of infusion is essential.Full instructions are given in the data sheet and package insert.

Preparation: The contents of four ampoules should be injected aseptically into one of the following: 0.9% Sodium Chloride Injection or 5% Dextrose Injection (500 or 250ml).

Recommended dosage for adults including the elderly: Infusion should begin at a dose of 0.5 µg/kg/min and may be increased to 1µg/kg/min and then in increments (0.5-1 µg/kg/min) up to 6 µg/kg/min at not less than 15 minute intervals, according to the patient's haemodynamic and clinical response. The rate of administration and duration of therapy should be adjusted according to the patient's response as determined by heart rate and rhythm (ECG), blood pressure, urine output and, whenever possible, measurement of cardiac output. Extended therapy beyond 48 hours has not been fully evaluated. It is recommended that the infusion of Dopacard is reduced gradually.

Contra-indications, Precautions, Warnings:

Contra-indications: Known hypersensitivity to dopexamine hydrochloride or excipients (disodium edetate). Concurrent MAOI administration, left ventricular outlet obstruction (such as hypertrophic obstructive cardiomyopathy or aortic stenosis), phaeochromocytoma, thrombocytopenia.

Precautions: If any correction of hypovolaemia is required this should be achieved before the administration of Dopacard.

Warnings: Dopacard should be administered with caution to patients with a clinical history of ischaemic heart disease especially following acute myocardial infarction or recent episodes of angina pectoris. A small, reversible fall in circulating platelet numbers has been observed in some patients. No adverse experiences attributable to alterations in platelet count have been seen in clinical studies. Plasma potassium may decrease and blood glucose may increase during Dopacard administration and care is required in its use in patients with, or at risk of, hypokalaemia or hyperglycaemia. In patients with a marked reduced systemic vascular resistance, Dopacard should not be used as a direct substitute for pressor agents or other inotropes. If cardiac arrhythmia should occur, the dosage should be reduced or infusion discontinued. There have been occasional reports of partial tolerance, with some attenuation of the haemodynamic response developing during long term infusions of Dopacard. The safety and efficacy of Dopacard for use in children has not been established.

Use in Pregnant and Lactating Women: Dopacard is not currently recommended for use in pregnant and lactating women.

Side effects: Dose-related increases in heart rate may occur during infusion of Dopacard; in most cases these are not clinically significant. Occasionally excessive tachycardia or ventricular extrasystoles, and, more rarely, atrial fibrillation, have been noted during the infusion, necessitating reduction or temporary discontinuation of the infusion. Tachycardia may be more pronounced in patients with pre-existing atrial fibrillation. The following side-effects have been reported infrequently, in most cases at high dosage: Nausea, vomiting, hypotension, dyspnoea, headache, hypertension, tremor, chest pain, cardiac failure, increased sweating, angina pectoris.

Interactions: Dopacard may potentiate the effects of exogenous noradrenaline and may attenuate the inotropic effects of higher doses of dopamine. Caution in the concomitant use of β_2 - adrenergic and dopamine receptor antagonists because of possible attenuation of the phamacological effects of Dopacard.

Product Licence No.: PL 6958/0008.

Legal Category: POM. **Name and Address of Product Licence Holder:** Porton Products Ltd., 1 Bath Road, Maidenhead, Berkshire SL6 4UH. Tel: (0628) 771417. **NHS Cost:** £18.94 per 5ml ampoule.

Further information is available in the data sheet or package insert, or on request from the product licence holder.

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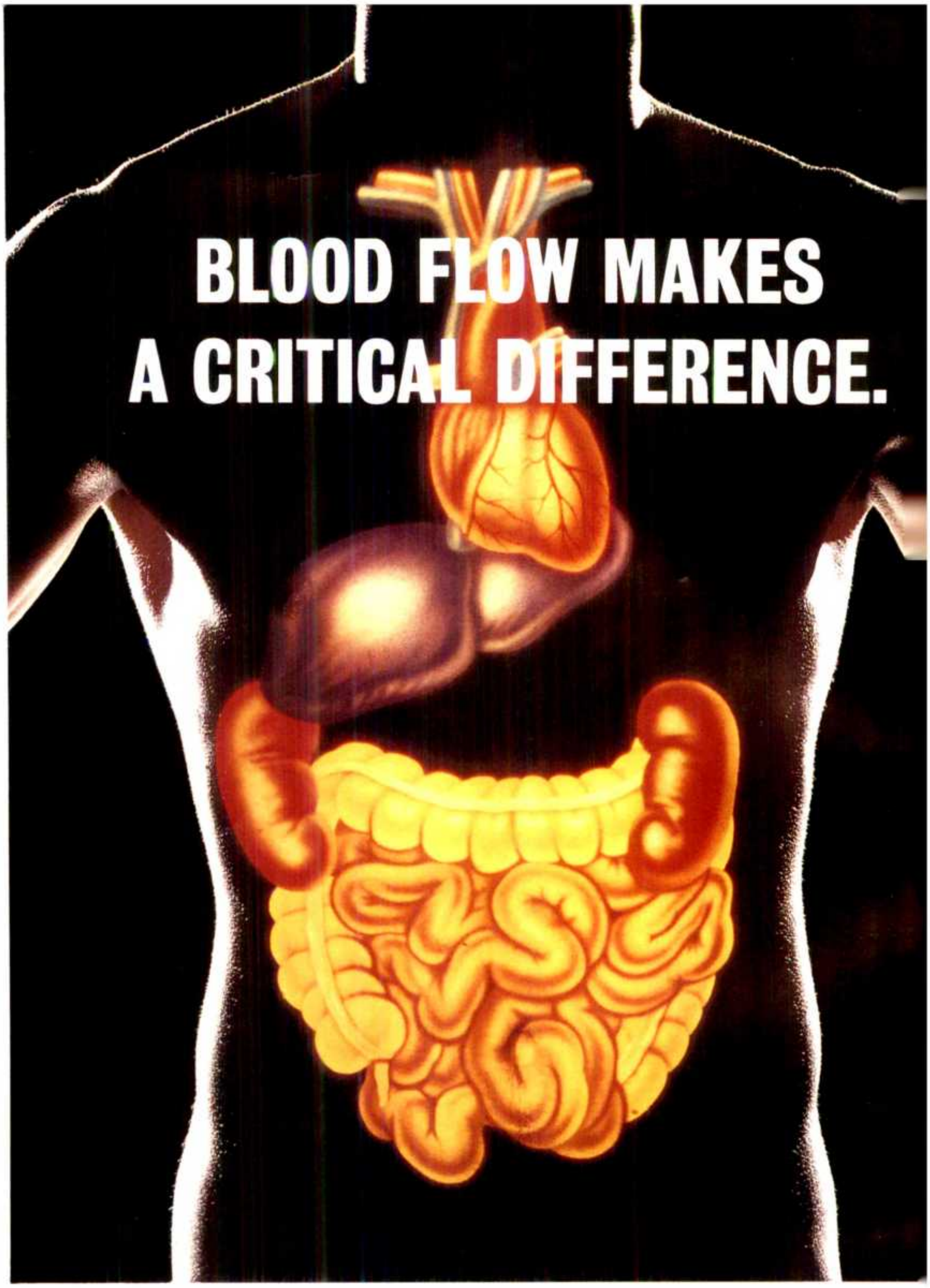

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The distribution of the increased cardiac output to vascular beds such as the kidney, liver and gut, without the risk of vasoconstriction, offers improved b flow to these vital organs.

DOPACAR
dopexamine hydrochlo

Increasing Renal and Hepato-Splanchnic blood fl

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' TABLETS
data sheet before prescribing)
tion White tablets containing the
of either 250mg, 500mg or 750mg
acin. **Uses** Ciprofloxacin is
for the treatment of single or mixed
caused by susceptible organisms.
icated for prophylaxis against
n elective upper gastro-intestinal
nd endoscopy where there is an
d risk of infection. **Dosage and**
tration The tablets should be
ed whole with liquid. ***Adults***:
mg twice daily. In surgical
xis a single 750mg tablet
ered 60–90 minutes before the
re (but see interactions with oral
ants). ***Duration of treatment*** For
ctions the usual treatment period is
days, except in cases of acute
cated cystitis where treatment is
vice daily for 3 days. Generally, in
d chronic infections where sensitivity
, treatment should be continued for
days after the signs and symptoms
on have disappeared. ***Elderly*** No
justment. **Contra-indications**
nsitivity to ciprofloxacin or other
es; also in children and growing
ents except where the benefits of
t outweigh the risks. **Warnings and**
ons Use with caution in epileptics
ents with a history of CNS disorders.
it could result in impairment of ability
or operate machinery. Crystalluria
n reported so patients should be well
d and excessive urine alkalinity
. As haemolytic reactions with
acin are possible in patients with
nd actual defects in glucose-6-
te dehydrogenase activity, use with
. **Drug interactions** Increased
levels of theophylline have been
d following concurrent administration
ofloxacin. The dose of theophylline
be reduced and plasma levels of
line monitored. Where monitoring of
levels is not possible, avoid the use
ofloxacin in patients receiving
line. Particular caution is advised in
atients with convulsive disorders.
tions have also been noted with
ulants and cyclosporin. The tablets
ot be administered within 4 hours of
tions containing magnesium,
um or iron salts. High doses of
nes have shown an interaction with
in animals leading to convulsions.
stration of quinolones and
amide simultaneously can potentiate
ect of glibenclamide, resulting in
ycaemia. Opiate premedicants or
l anaesthetic agents must not be
tered concomitantly with ciprofloxacin
sed for surgical prophylaxis. **Use in**
ancy and lactation Not
mended. **Side-effects** Gastro-
nal, CNS, hypersensitivity/skin
s, musculoskeletal and special sense
ances. Renal and hepatic
ances. Effects on haematological
eters. Also reported vasculitis,
membranous colitis, Stevens-Johnson
ome, Lyell Syndrome, haemolytic
ia, granulocytopenia, intracranial
ension, petechiae, haemorrhagic
tenosynovitis and tachycardia.
sage Serum levels of ciprofloxacin
luced by dialysis. **Legal category**
Package quantities Blister strips of
packs of 10, 20, and 100 tablets.
ct licence numbers PL0010
148. **Basic NHS cost** 250mg x 10
£7.50, 500mg x 10 tablets £13.75,
x 10 tablets £20.00. **Date of**
tion July 1993

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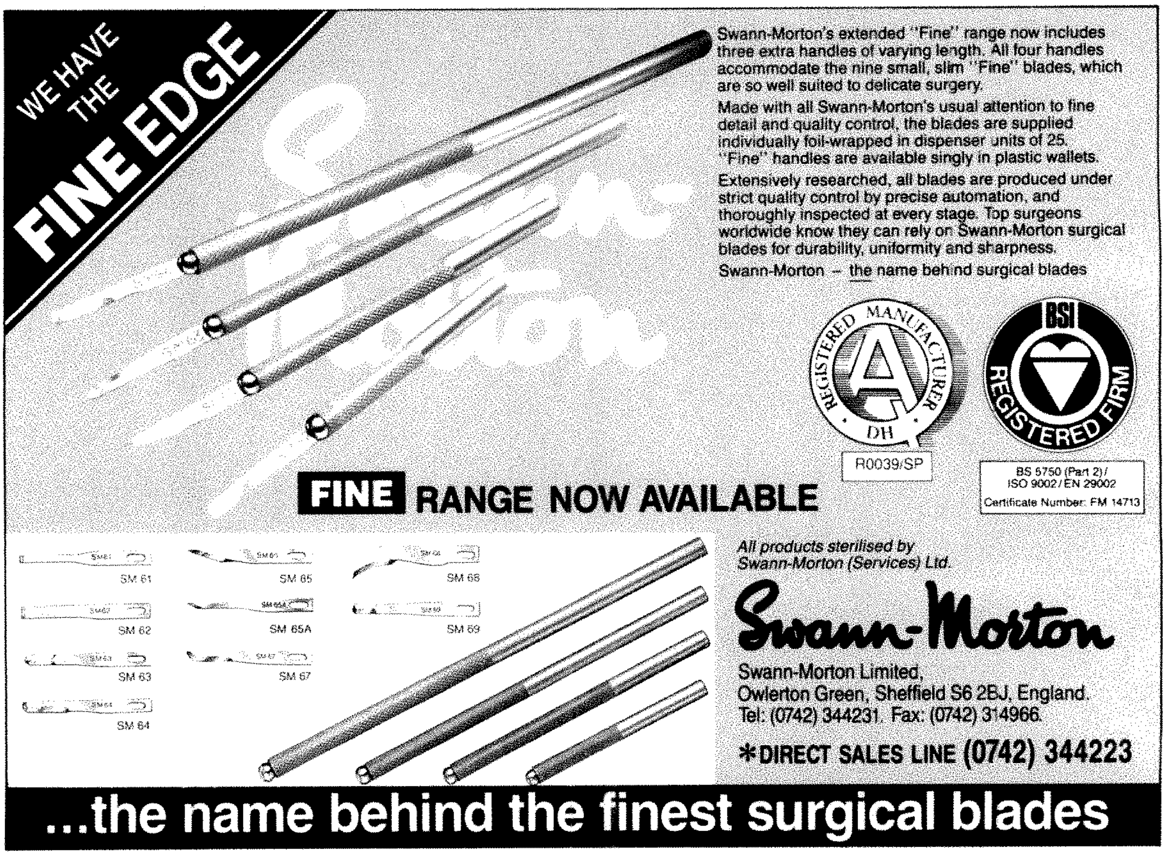

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12.30	LUNCH	
1.30	Duty of a Referee	A. Pollock
2.15	Editing a Journal	J. Smith
3.00	Publishing a Journal	R. Williamson
4.00	Editing a Book	A. Nicolaides
4.45	How a technical Editor can help	M. Evans

Friday 11 March 1994

10.00	Statistical considerations in communicating Medical Science	H.A.F. Dudley
10.45	Word Processors	J. Dorner
11.30	Design of Clinical Trials	H.A.F. Dudley
12.30	LUNCH	
1.30	Writing a thesis	H.A.F. Dudley
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3.00	Giving a Lecture	P. Chu

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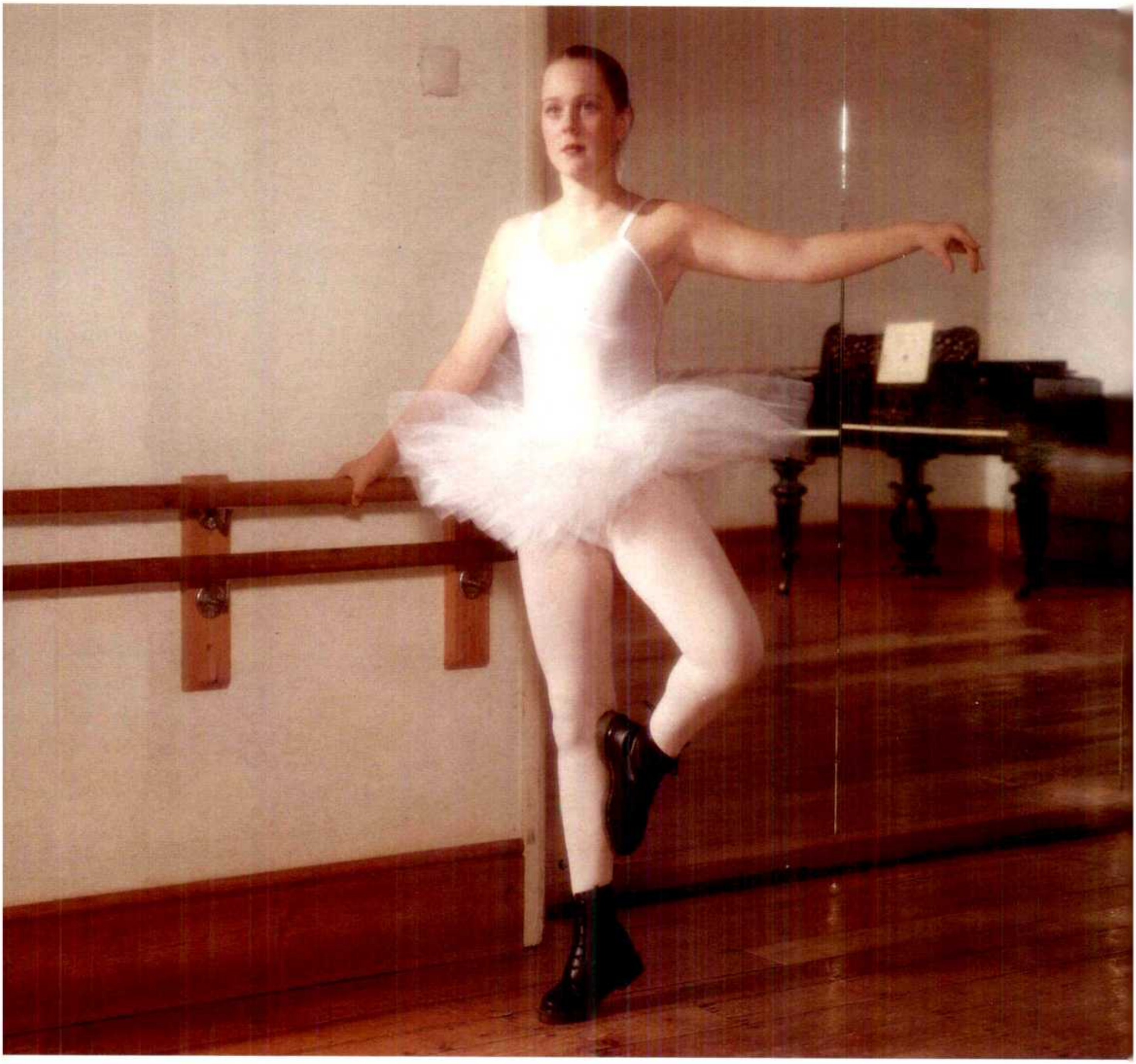

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MR CHRISTOPHER RUSSELL

(London)

Ronald Christopher Gordon Russell (born 1940) is a consultant surgeon at the Middlesex Hospital, London, where he graduated MB BS in 1963. Obtaining his FRCS in 1966 and MS (London) in 1979, he became a senior registrar at the Central Middlesex Hospital and later a consultant senior lecturer at St Mary's Hospital, London. His special interest is in hepatobiliary and pancreatic surgery. Chris Russell has been a loyal servant of *The British Journal of Surgery* for many years. He first joined the Editorial Committee and Council of the BJS Society in 1977, becoming Assistant Editor in 1978, Associate Editor in 1981 and then Joint Editor with David Carter from 1986 to 1991. We welcome him back to the Editorial Committee and Council and are counting on his further advice and support.

DR STEPHEN LOWRY

(USA)

Stephen F. Lowry (born 1947) is Professor of Surgery and Director of the Laboratory of Surgical Metabolism at Cornell University Medical College. He graduated from the University of Michigan in 1973 and completed his general surgical training at the University of Utah. He was a Clinical Associate and Investigator at the National Cancer Institute and a Surgical Fellow at the Memorial Sloan–Kettering Cancer Center, where he also holds an appointment. His research interests lie in nutritional biochemistry, oncology and infection; he has made several contributions to the emerging area of cytokine biology in surgical disease.

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MR JACK COLLIN
(Oxford)

Jack Collin was born in 1945, qualified with Honours at Newcastle upon Tyne in 1968 and trained in Newcastle and the Mayo Clinic, USA. He is Reader in Surgery at the University of Oxford and a consultant surgeon at the John Radcliffe Hospital. At The Royal College of Surgeons of England he has been Arris and Gale Lecturer (1976), Jacksonian Prize winner (1976) and Hunterian Professor (1988). He has also been Moynihan Fellow (Association of Surgeons) and James IV Travelling Fellow. His clinical and research interests are in vascular surgery.

PROFESSOR ULF HAGLUND
(Sweden)

Ulf Haglund was born in 1944 and graduated from Göteborg University in 1971. He trained in Göteborg, where he obtained a PhD, then moved to Lund as Associate Professor (1982–1987). He took up his present post as Professor and Chief of Surgery at the University Hospital, Uppsala in 1988. His clinical interests are centred on the upper gastrointestinal and pancreatobiliary tracts, and he has a strong research interest in septic shock. He is current President of the Swedish Surgical Society.

Robin Williamson

Br. J. Surg. 1993, Vol. 80, December, 1499–1500

Acute pancreatitis: the value of life

Those of us who work in the financially constrained and increasingly cost-conscious National Health Service are all too well aware of the increasing need to justify our use of resources. Two papers in this issue of the *Journal* address the important question of cost–benefit relationships in the treatment of patients with acute fulminant or necrotizing pancreatitis, a severe and life-threatening disease that is estimated to account for some 15 per cent of all attacks of acute pancreatitis[1]. In recent years there have been significant advances in our ability to detect and assess the severity of necrosis, notably by dynamic contrast-enhanced computed tomography (CT); improvements in patient care and surgical management have resulted in mortality rates that may be as low as 8 per cent[2] but which are generally of the order of 25 per cent[3]. These patients often remain grievously ill for prolonged periods, require intensive care and/or high-dependency nursing, and frequently need multiple operations and related procedures. Is it all worthwhile?

From the outset, it is incontestable that patients with acute necrotizing pancreatitis consume a great deal of resource. Fenton-Lee and Imrie[4] from Glasgow have attempted to cost the management of ten such patients admitted in the 12-month period to August 1991. The patients appear representative of UK practice in this context in that they had a median age of 63 years, gallstones were implicated in seven cases and alcohol in three, and all had severe disease on admission as assessed by scoring of prognostic factors. All had pancreatic or peripancreatic necrosis on bolus intravenous contrast-enhanced CT, although the extent of involvement was not defined, and in six patients there was proven infected necrosis. Consumption of resources was predictably high and was reflected in a median stay in intensive care of 7 days and a hospital stay ranging from 40 to 150 days. Our own record for hospital stay in such patients currently stands at 226 days, and I suspect that many readers will be able to furnish even more impressive evidence of the fortitude and indestructibility of the human organism.

With regard to costing, one still has misgivings about the current degree of sophistication of hospital cost computation in this country, feelings underlined by the admission that the cost of endoscopic procedures in the Glasgow experience was not available from the health board concerned. Nevertheless, within the limits of computational error, the total estimated cost per patient in the Glasgow series averaged no less than £18 441 (range £9296–£33 796), two-thirds of this being attributable to hospitalization excluding the cost of investigations, operations and procedures.

The Glasgow group also attempted to relate outcome to the quality of life achieved by patients by a brave foray into the minefield of the quality-adjusted life year (QALY). As always in such endeavours, one must take a great deal on trust. The key disability and distress index at the time of admission was assessed by the senior surgeon whereas, in the ideal world, a disinterested third party might be preferred. It is assumed that all patients would have died without treatment, a contention that might be challenged by some with respect to those with sterile necrosis[5], and that all patients who survived would have a normal life expectancy of 75 years, a postulate that might give rise to some doubts in the case of the 29-year-old Glasgow man with necrotizing pancreatitis attributable to alcohol. Within these stated restrictions, the authors estimated that the mean number of QALYs obtained was 8·55, at a mean cost per QALY of £2157. In my admittedly less than objective view as a surgeon with a major interest in pancreatic disease this seems a perfectly reasonable use of resources and one that the patients, their relatives and the community in general would almost certainly endorse. As with all blunt instruments, the analysis must be wielded carefully, and I have no doubt that recipients of renal transplants and their relatives would not warm to the notion that the management of acute necrotizing pancreatitis is 'more favourable' in cost–benefit terms than that of kidney transplantation at a 1988 price of £6072 per QALY gained.

The second paper dealing with this question moves away from the treacherous ground of QALYs to assess a series of Finnish patients an average of 6·2 years after an attack of fulminant pancreatitis[6]. The two patient populations are not strictly

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comparable; the Finnish patients were recruited over a longer period, alcohol was the aetiological factor in three-quarters of cases and patients were younger. In addition, fewer than 60 per cent of the Finnish patients had severe disease on Ranson scoring and conservative treatment with peritoneal lavage was the mainstay of therapy, at least in the first instance. No fewer than one-third of patients died in hospital, underlining the potentially lethal nature of this disease. Of the 37 survivors assessed, 30 were regarded as in 'good' or 'normal' condition but, more reliably, 24 were working. Diabetes was present in 20 patients of whom nine needed insulin, and the paper emphasizes the fact that formal resection should now be avoided in favour of blunt necrosectomy if surgical intervention becomes necessary. Not only is resection the more dangerous option[3], it is clear that it often results in inappropriate removal of viable pancreas in patients who may prove to have little functional pancreatic reserve. These factors have particular importance in patients with alcohol-associated disease, in which it is now appreciated that there may be underlying chronic damage and that the gland often does not return to anatomical and functional normality. It is noteworthy that, of the patients with frank diabetes or abnormal glucose tolerance at follow-up in the Finnish experience, no fewer than 88 per cent had suffered from alcohol-associated pancreatitis.

It is clear that the great majority of patients can now be expected to survive an attack of acute necrotizing pancreatitis, and in my view the expenditure and use of resources seem eminently justifiable. Long-term survival and acceptable quality of life can be anticipated, and one must agree with the Finnish authors when they conclude that patients with acute fulminant pancreatitis are 'definitely worth treating'. In many ways the need to make such statements is a sad commentary on the current requirement to defend management decisions in an era when the accountant reigns supreme. It is now being debated whether some patients with 'self-inflicted' disease attributable to tobacco smoking or alcohol abuse should be denied treatment when resources are restricted. Patients with alcohol-induced pancreatitis are in danger of falling into this modern trap; it is salutary to learn that in the Finnish experience two-thirds of the previously heavy drinkers had either reduced their intake considerably or had become abstainers. Assuming that Finnish patients are to be trusted when asked about their alcohol consumption, it may be that surviving an attack of acute necrotizing pancreatitis leads to a radical adjustment of lifestyle which results in increased longevity and improved life quality. Life is surely so precious that resources must continue to be made available to patients with acute necrotizing pancreatitis.

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'Damage control' in trauma surgery

The introduction of increasingly complex surgical solutions to severe truncal injuries was a salient feature of trauma surgery during the 1960s and 1970s. Major operations, such as formal hepatic resection or pancreatoduodenectomy, were reported with an acceptable mortality rate, reflecting the prevailing belief that complex surgery, when necessary, is a feasible option in difficult trauma situations. Advances in modern anaesthesia, autotransfusion and critical care contributed to this view.

During the past decade, it gradually became apparent that the results of these prolonged and extensive procedures in the critically injured were often poor, even in experienced hands[1]. Despite technological advance, the operating room remains a physiologically unfavourable environment for the severely injured patient. This is because laparotomy for major trauma involves dissipation of body heat and blood loss requiring massive replacement. The result is rapid development of hypothermia, coagulopathy and metabolic acidosis[2]. A vicious circle is set up in which these three elements augment each other, leading to death from an irreversible physiological insult[3]. The triad of hypothermia, coagulopathy and metabolic acidosis effectively marks the limit of the patient's ability to cope with the physiological consequences of injury; crossing this limit will frustrate even the most technically successful repair. Unfortunately, in severe trauma the time available for repair of injuries is inversely related to their severity.

These observations have led to the development of a new surgical strategy that sacrifices the completeness of the immediate repair so as adequately to address the combined physiological impact of trauma and surgery. During the initial operation, the surgeon does only the absolute minimum necessary rapidly to control exsanguination and to prevent spillage of intestinal content and urine into the peritoneal cavity. Complex or time-consuming procedures, such as formal resection and reconstruction, are deliberately avoided in haemodynamically unstable patients[4]. Definitive repair of the injured organs is postponed until reoperation can be performed on a stable, non-bleeding and warm patient with optimized oxygen delivery. This management concept has been termed 'damage control' or 'planned reoperation'.

Techniques for abbreviating the surgical procedure in unstable patients are very straightforward. One traditional method for the management of major liver injuries is packing. There is no reason why the same method should not apply to other technically challenging situations such as retrohepatic venous injury[5] or retroperitoneal and pelvic haemorrhage[6]. Examples of simple techniques to buy time besides packing include temporary closure of the lumen of injured bowel without resection[4], tying off or rapid exteriorization of an injured ureter, non-anatomical lung resection with a linear stapler, insertion of temporary vascular shunts[7] and balloon tamponade of bleeding cavities or inaccessible vessels[8]. Since the patient will require reoperation, formal closure of the chest or abdomen is unnecessary; skin closure using only a running stitch or towel clips saves valuable time[9]. The fascia is left untouched and preserved until a later formal closure. In some patients, massive visceral oedema will prevent skin approximation. Under these circumstances, temporary abdominal closure with a soft plastic sheet[4,9] or synthetic mesh[10] is the only practical option.

Despite its simplicity and logic, this new approach is being adopted only slowly. This is because the abrupt termination of an operation to prevent an as yet unapparent physiological insult seems to contrast with traditional surgical values. It is only during the past 2 years that reports have started to emerge on the use of 'damage control'[4,6,9–12].

The original application of this concept was in critically ill patients who already exhibit intraoperative warning signs such as coagulopathy, indicating that they are approaching or have passed their physiological limits. It seems that the key to successful application of the planned reoperation approach hinges on an early decision to employ it within the first few minutes of the initial operation, when the surgeon estimates that the patient will not tolerate a definitive procedure. This decision must be based on realistic evaluation of the extent of the necessary repair and of the patient's physiological reserves.

Adoption of this new management strategy brings with it a host of medical and logistic problems. Accident and emergency referral centres must make arrangements for a strategy that includes a quick primary operation followed by a prolonged stay

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in the intensive care unit and planned – or sometimes unplanned – reoperation(s). Some patients continue to bleed after surgery, requiring a decision about the feasibility of re-exploration. In others, increased intra-abdominal pressure from distended and oedematous bowel impairs ventilation and renal function, requiring immediate decompression[12,13]. All of this translates into a vast investment of hospital resources in a small group of severely injured patients and, although the results obtained using the new approach are superior to those of the traditional method, the mortality rate is still 30 per cent or higher[4,6,10–12].

The principles of planned reoperation for trauma are eminently applicable to hospitals in rural areas, to surgeons who encounter major trauma infrequently, and to field surgery during war. A short life-saving procedure, followed by transfer to an accident and emergency referral centre for continued management and planned reoperation, is clearly in the patient's best interest under these circumstances.

The new 'damage control' concept is likely to modify the management of the critically injured. Surgeons from all specialties involved in trauma care will adapt to the new strategy by developing appropriate surgical solutions for injuries in their respective fields. All medical personnel caring for wounded patients should be familiar with this new concept and its surgical and logistic implications.

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Role of the leucocyte in the pathogenesis of vascular disease

The leucocyte plays a key role in the local and systemic tissue injury that results from peripheral arterial disease and chronic venous insufficiency. Despite the apparent dissimilarities between limb ischaemia and chronic venous ulceration, in both diseases macrovascular abnormalities lead to microvascular leucocyte trapping and activation. Activated leucocytes adhere to and damage adjacent endothelium by expressing adhesion molecules and releasing harmful moieties such as proteases and free radicals. Subsequent loss of endothelial integrity and the migration of activated leucocytes outwith the circulation leads to destruction of surrounding tissue. Leucocytes and their products are also involved in the systemic manifestations of ischaemia such as multiple organ failure and coagulopathy. An overview of leucocyte biology as it pertains to peripheral arterial and venous disease is presented. The opportunities for novel therapeutic interventions based on a better understanding of this biology are also discussed.

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Little is known of how peripheral arterial disease and chronic venous insufficiency lead to the local tissue destruction seen so commonly in everyday clinical practice. The systemic manifestations of vascular disease such as multiple organ failure and coagulopathy are also poorly understood. It is thus not surprising that our ability to limit these processes, while corrective surgical measures are undertaken, is extremely restricted. For example, compression therapy for venous ulceration is associated with a high rate of recurrence[1], and for the majority of patients with critical limb ischaemia the only hope of arresting progressive tissue loss rests with some form of local surgical reconstruction. Nevertheless, the commonly observed mortality from myocardial infarction and stroke in patients with peripheral arterial disease clearly indicates that this is a generalized condition that requires systemic treatment[2].

Increasing evidence points to a central role for abnormal leucocyte–endothelial cell interactions in the pathogenesis of, and tissue destruction resulting from, these conditions[3–5]. Although the present review deals solely with peripheral arterial and venous disease it is likely that similar mechanisms are involved in myocardial and cerebral ischaemia. It has been known for some time that a raised white cell count is associated with vascular disease in the coronary, cerebral and peripheral circulations[6,7]. This association appears to be independent of other known risk factors, such as smoking, that also promote leucocytosis[8]. More recently, it has been discovered that leucocytes are sequestered in ischaemic muscle and in the legs of patients with chronic venous insufficiency (*Figure 1*). In both situations sequestration is postulated to lead to (or result from) activation of leucocytes, which in turn results in the generation of free radicals[9], proteases, histamine[10], neutrophil chemoattractants[11] and complement[12]. These substances destroy the endothelium and its basement membrane, increase vascular permeability and derange microcirculatory flow[13,14]. Such chronic recurring inflammation may also be important in the development of atherosclerosis itself[15,16]. Activated leucocytes also interact with platelets, erythrocytes and components of the coagulation–fibrinolysis pathways to promote microvascular thrombosis[17,18]. Leucocytes also mediate the systemic complications of vascular disease such as adult respiratory distress syndrome (ARDS)[19–21], endotoxaemia[22] and disseminated intravascular coagulation[23]. Activated endothelial cells play an equally important role in these pathological processes by releasing substances such as platelet-activating factor (PAF), thromboxanes and cytokines that attract and activate leucocytes and platelets.

It is the aim of this paper to review leucocyte biology as it pertains to the pathogenesis of local and systemic tissue damage

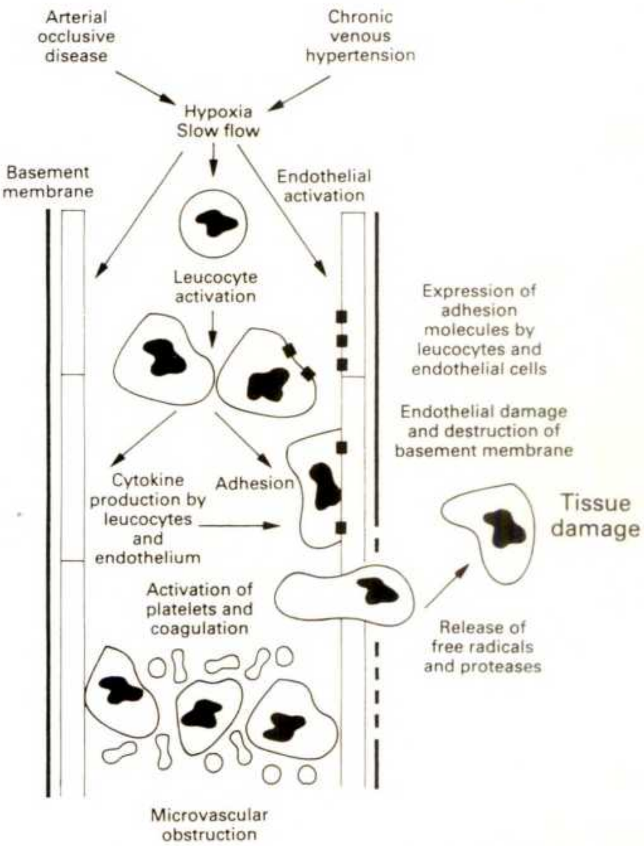
Arterial occlusive disease
Chronic venous hypertension
Hypoxia Slow flow
Basement membrane
Endothelial activation
Leucocyte activation
Expression of adhesion molecules by leucocytes and endothelial cells
Endothelial damage and destruction of basement membrane
Cytokine production by leucocytes and endothelium
Adhesion
Tissue damage
Activation of platelets and coagulation
Release of free radicals and proteases
Microvascular obstruction

Figure 1 *White cell trapping and activation in venous and arterial disease*

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consequent on peripheral arterial disease and chronic venous insufficiency. In particular, novel therapeutic interventions that might act through modifying leucocyte activity are discussed.

Leucocyte–endothelial cell pathophysiology

A complex and finely balanced relationship exists between the cellular and humoral components of blood and the endothelial cells that line the vasculature. This relationship plays a vital role in preserving normal blood flow and in orchestrating appropriate, as well as preventing inappropriate and potentially harmful, inflammatory and thrombotic responses[24].

Mononuclear and polymorphonuclear leucocytes

Mononuclear phagocytes arise in the bone marrow, circulate in the blood as monocytes and then enter the tissues to become macrophages. Both cell types may become activated in response to a variety of stimuli, following which they are capable of phagocytosing and destroying antigen. Activated cells also present antigen to lymphocytes, so allowing a specific immune response to be initiated. Polymorphonuclear granulocytes account for 50–70 per cent of all circulating leucocytes and neutrophils comprise 90 per cent of all granulocytes. Like mononuclear cells, neutrophils normally circulate in a quiescent state but when activated are capable of adhering to endothelium, entering tissues and releasing a variety of noxious substances recognized for their ability to cause tissue damage. For example, neutrophil elastase digests elastin, fibronectin, fibrinogen and collagen, and leads to destruction of the basement membrane, increased endothelial adhesiveness and permeability and oedema. In addition, because they are much less deformable than erythrocytes[25,26] and because they adhere to endothelial cells[27,28], activated leucocytes may obstruct the microvasculature[29,30].

Endothelial cells

Endothelial cells release a wide range of biologically active factors such as endothelium-derived relaxing factor (EDRF), which relaxes smooth muscle[31], endothelin, a powerful vasoconstrictor[32], thrombomodulin and prostacyclin, which maintain a non-coagulant surface[33], cytokines, such as interleukin (IL) 1, which attract and activate leucocytes, and adhesion molecules that mediate interaction with leucocytes. Together these moieties control blood flow, coagulation and fibrinolysis, as well as leucocyte margination, activation and diapedesis. Some or all of these properties may be lost or modified in the presence of hypoxia and in low-flow states[34–36].

Cytokines

The cytokines are a family of low molecular weight peptides that are released by and act on a wide range of cells including leucocytes and endothelial cells[37,38]. They play a central role in generation of the inappropriate inflammatory responses resulting from the abnormal leucocyte–endothelial cell interactions present in vascular disease. For example, IL-1 and tumour necrosis factor (TNF) are released from activated mononuclear cells and act on endothelial cells to suppress anticoagulant activity, induce procoagulant activity and promote the production of PAF, colony-stimulating factor (CSF)[39] and IL-6[40]. IL-1 causes neutrophilia, thrombocytosis[41] and vasodilatation through stimulating endothelial cells to produce nitric oxide and EDRF[42]. IL-1 is also implicated in the pathogenesis of atherosclerosis through promoting vascular smooth muscle proliferation and the formation of fatty plaques[43]. TNF increases endothelial cell susceptibility to immune attack, is directly toxic to capillary endothelium[44], promotes the release of CSF by endothelial cells and is angiogenic[45]. Both IL-1 and TNF stimulate neutrophil and lymphocyte adhesion to endothelial cells[46,47]. They also stimulate transendothelial migration of neutrophils and act as modulators of prostacyclin synthesis by endothelial cells[48]. IL-2 may increase prostacyclin synthesis and enhance leucocyte adhesion and endothelial cell growth. IL-4 may be an important regulator of endothelial cell morphology and proliferation as well as acting as a potent lymphocyte growth factor[49]. IL-6 is produced by endothelial cells in response to IL-1 and TNF, and is a major stimulus of the acute-phase response. IL-6 also primes neutrophils for their respiratory burst and release of free radicals[50]. This interleukin is likely, therefore, to be important in the pathogenesis of the systemic manifestations of ischaemia[51]. IL-8 may also be important in the development of such systemic manifestations. Cultured endothelial cells have receptors for transforming growth factors and these peptides appear to have an inhibitory action on endothelial cell growth, as well as reducing the increase in adhesivity of endothelial cells for leucocytes caused by IL-1 and TNF. Endothelial cells also produce interferons, in response to which they increase expression of the class I major histocompatibility antigens and their adhesivity for lymphocytes. Interferons also inhibit endothelial cell growth and induce the expression of other cytokines, complement factors and adhesion molecules. Granulocyte and monocyte CSF are mitogenic for endothelial cells[52].

Complement

The complement cascade is a series of plasma proteins that are sequentially activated by a range of stimuli such as bacterial infection and tissue hypoxia. Two main products, the anaphylotoxins C3a and C5a, increase vascular permeability, activate leucocytes and interact with the kinin, coagulation and fibrinolytic systems to promote intravascular thrombosis and inflammation. Complement activation may also be important in the systemic effects of ischaemia such as ARDS[53]. Ischaemia–reperfusion injury of skeletal muscle also results in the activation of complement[54,55].

Adhesion molecules

Leucocytes and endothelial cells express adhesion molecules that control leucocyte adhesion within the circulation and migration into perivascular tissue[56–61]. Adhesion molecules on leucocytes comprise the selectins and integrins, whereas endothelial cells express selectins and adhesion proteins belonging to the immunoglobulin family[62]. Binding of adhesion molecules is also the trigger for leucocyte degranulation, the oxidative burst and generation of free radicals[63]. Expression of adhesion molecules changes rapidly with the activation status of both leucocytes and endothelial cells[64]. For example, stimulation of neutrophils by chemoattractants rapidly activates the integrins and endothelial expression of adhesion molecules is increased by thrombin[65] and various cytokines such as IL-1 and TNF[66]. Expression of adhesion molecules leads to leucocyte emigration within inflamed vessels *in vivo*[67]. Adhesion molecules may also be shed from the cell and increased levels are found in the serum of patients with septic shock; in these circumstances they may be a measure of excessive or inappropriate endothelial or leucocyte activation[68].

Free radicals

Free radicals are generated by phagocytes, through the action of membrane-bound oxidases and myeloperoxidase, and by endothelial cells through the action of xanthine oxidase, which is formed from xanthine dehydrogenase in hypoxic conditions. As ischaemia progresses, adenosine 5′-triphosphate is degraded to hypoxanthine. This is then converted to uric acid by xanthine oxidase with production of the highly reactive superoxide anion. Free radical damage may be particularly important during reperfusion of ischaemic muscle or skin as levels of xanthine and oxygen are both high at this time.

Free radicals damage cells through peroxidation of membrane phospholipids and denaturation of macromolecules[69]. Free radicals impair endothelial function by reducing prostacyclin and increasing thromboxane production, promoting the breakdown of EDRF, inhibiting antithrombin III activity and promoting cholesterol deposition[70]. Free radicals may therefore be involved in both acute and chronic arterial disease[71]. Free radical toxicity is normally limited by scavengers such as superoxide dismutase, glutathione and caeruloplasmin. In ischaemic tissue, levels of these protective substances are reduced and evidence of excess lipid peroxidation and increased plasma viscosity can be detected in patients with peripheral vascular disease. For example, limb swelling after femoropopliteal bypass has been attributed to the generation of free radicals[72]. Free radicals may also be involved in the pathogenesis of venous ulceration[73].

Platelets

There is a complex interaction between platelets, leucocytes and endothelial cells in both health and disease[74]. Normal endothelial cells produce a range of 'protective' moieties such as prostacyclin, EDRF, adenosine diphosphatase and thrombomodulin that prevent platelet adhesion. Although EDRF production is constitutive it is also inducible by cytokines[75] such as IL-2. EDRF production is reduced in peripheral vascular disease because of both decreased synthesis and increased degradation such that vessels are incapable of endothelium-dependent vasodilatation. Adenosine diphosphatase breaks down adenosine 5'-diphosphate, a powerful cofactor in platelet stimulation by plasmin, to inactive adenosine 5'-monophosphate[76]. Thrombomodulin is an endothelial cell surface protein that inactivates thrombin, so preventing it from activating platelets, and activates protein C, a natural anticoagulant[77]. By contrast, platelets bind readily to damaged endothelial cells and subendothelial tissue. Adhesion is partly dependent on expression by endothelial cells of platelet–endothelial cell adhesion molecules[78]. Platelets also bind to endothelial cells indirectly by first adhering to activated neutrophils and monocytes, which in turn bind to endothelial cells via their own adhesion molecules[79]. Platelets also influence endothelial cell function by generating vasoactive substances such as lipoxin A_4, a vasodilator, and leukotriene C_4, a vasoconstrictor, from neutrophil precursors[80]. Platelets release plasminogen activator inhibitor 1, which neutralizes endothelium-derived plasminogen activator so reducing fibrinolysis. Platelet activation also enhances the production of endothelin 1 from activated endothelial cells. Endothelin 1 is a powerful vasoconstrictor and its levels are raised in atherosclerosis[81]. Activation of endothelial cells leads to the release of PAF, which causes vasoconstriction, platelet aggregation, and platelet and neutrophil adhesion to endothelial cells[82].

Venous disease

Venous ulceration results from sustained venous hypertension, which in turn arises from deep and/or superficial valvular incompetence. These macrovascular abnormalities lead to disruption of the microvasculature and a wide variety of abnormalities have been described in the tissues surrounding venous ulcers[83]. Dermal capillaries become tortuous and elongated (and thus may appear more numerous) and so present an increased surface area of endothelium to the circulating blood[84,85]. Intravascular thrombosis and platelet trapping[86], pericyte disruption[87], increased capillary permeability and abnormalities of lymphatic drainage have also been described. How these abnormalities are related to the process of skin ulceration is uncertain. The validity of early theories implicating skin hypoxia secondary to either stagnant desaturation, arteriovenous shunting or the formation of a fibrin cuff has been questioned[88–90]. More recently, it has been discovered that normal subjects sequester white cells in the legs if these are held dependent and motionless[91]. In similar studies patients with chronic venous insufficiency trapped far more leucocytes than normal controls[92]. This led to the proposal that venous hypertension leads to morphological changes in the microvasculature such that leucocytes are trapped and activated[3]. Trapped cells are poorly deformable, adhere to activated and damaged endothelium, and release proteolytic enzymes and free radicals that are directly harmful to tissues. This process has been likened to a form of ischaemia–reperfusion injury. Interestingly, compression hosiery appears to reduce leucocyte trapping within the leg, although it is not clear how this is achieved. The precise mechanism by which leucocytes become trapped within the legs of patients with chronic venous insufficiency and ulceration remains poorly defined. It is uncertain, for instance, whether leucocytes enter an abnormal microcirculation and become activated *in situ* or whether there is a degree of systemic activation that predisposes them to trapping within the leg. It is also unclear whether the trapped cells are predominantly monocytes or neutrophils. Most studies to date have examined leucocytes derived from the venous outflow of the leg, although it would not be unreasonable to presume that the maximally activated leucocytes, and thus those most worthy of study, remain in the affected area. Furthermore, although derangement of endothelial function is likely to be the primary abnormality, endothelial cell biology has been the subject of relatively little study. Immunohistochemical studies have confirmed that there is an excess number of leucocytes, predominantly monocytes and lymphocytes, in the skin of the gaiter area of patients with lipodermatosclerosis and healed venous ulcers[93,94]. However, in acute experimental venous hypertension, levels of products specific to neutrophil activation such as lactoferrin are raised in the effluent blood. One might therefore speculate that venous hypertension results in *chronic* monocyte trapping in the postcapillary venules of the leg, which in turn leads to generation of a range of cytokines that, perhaps following dependency, causes *acute* recruitment of neutrophils and subsequent tissue damage (*Figure 2*). Monocytes also appear to use neutrophils as the final instruments of tissue destruction in ischaemic tissue damage, as discussed below. Further studies examining the local milieu in terms of cytokine and adhesion molecule expression by leucocytes and endothelial cells are required to clarify these points.

Arterial disease

In addition to the macroscopically apparent effects of atherosclerosis, vascular spasm, platelet thrombus and embolism, ischaemic tissue damage occurs as a result of

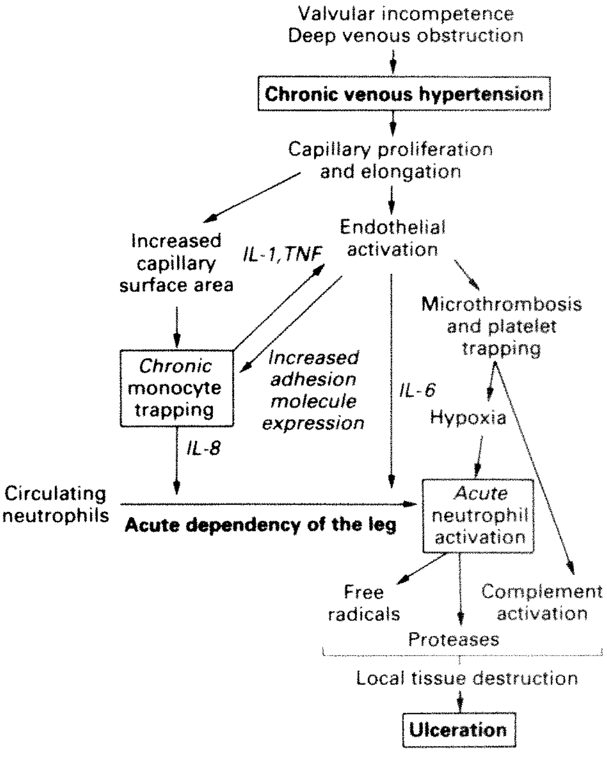
Valvular incompetence
Deep venous obstruction
Chronic venous hypertension
Capillary proliferation and elongation
Increased capillary surface area
Endothelial activation
IL-1, TNF
Microthrombosis and platelet trapping
Chronic monocyte trapping
Increased adhesion molecule expression
IL-6
Hypoxia
IL-8
Circulating neutrophils
Acute dependency of the leg
Acute neutrophil activation
Free radicals
Complement activation
Proteases
Local tissue destruction
Ulceration

Figure 2 *The pathogenesis of venous ulceration: a hypothesis. IL, interleukin; TNF, tumour necrosis factor*

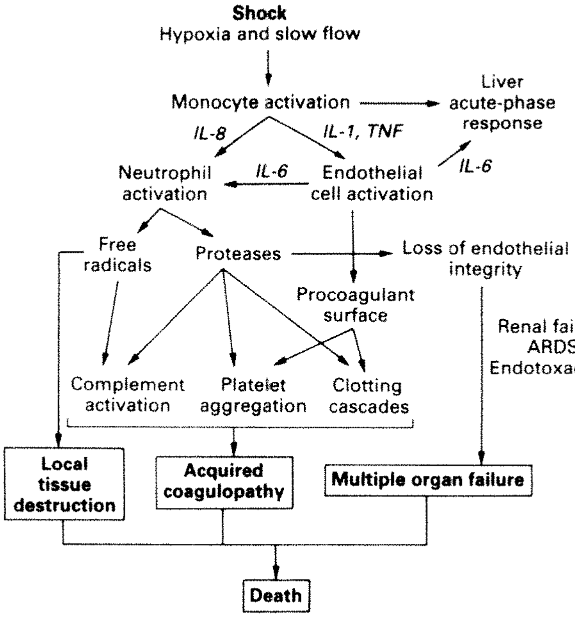

Figure 3 *The pathogenesis of multiple organ failure and coagulopathy in patients with ruptured aortic aneurysm: a hypothesis. IL, interleukin; TNF, tumour necrosis factor; ARDS, adult respiratory distress syndrome*

microvascular changes not unlike those found in chronic venous insufficiency. Although it has been known for many years that ischaemic infarction is associated with rapid neutrophil accumulation, recent evidence suggests a wider and earlier role for leucocytes in ischaemic disease. There is good evidence for a state of chronic white cell activation in patients with arterial disease; raised plasma thiol and thromboxane levels, an increased leucocyte count, depressed fibrinolytic activity, and activation of complement and free radicals are found both before and after prosthetic vascular reconstruction[95]. The histamine and alkaline phosphatase content of leucocytes is increased in ischaemic disease[10]. Patients with vascular disease therefore suffer from a prolonged but low-grade 'acute-phase reaction'[96]. As in venous disease, one of the key events in ischaemic tissue damage appears to be microvascular obstruction by activated leucocytes. Neutrophils are 2000 times less deformable than red blood cells and in ischaemic conditions extend pseudopodia, aggregate and demonstrate increased endothelial adhesiveness[97]. Once lodged in the microcirculation, activated neutrophils cause loss of endothelial integrity, secondary thrombosis and irreversible vessel occlusion.

In animal models neutrophil rolling, endothelial swelling and vascular leakage occur following experimentally induced claudication. Similar changes are seen in the contralateral unaffected leg, suggesting a systemic response to local ischaemia[98]. In patients with intermittent claudication, exercise is associated with increased urinary albumin excretion (a reflection of vascular permeability), decreased neutrophil filterability, and increased serum lysozyme activity[99,100]. Claudicants demonstrate a rise in levels of serum thromboxane A_2 and urinary thromboxane metabolites after exercise[101,102]. Calf pain in patients with claudication is associated with a significant decrease in leucocyte deformability[103,104]. These exercise-related manifestations of systemic inflammation and neutrophil activation disappear after successful arterial bypass. Patients with critical limb ischaemia leading to amputation also demonstrate neutrophil activation and loss of deformability[105,106]. White cell rheology returns to normal following surgery and healing.

In addition to the period of ischaemia it is clear that significant tissue damage is sustained following reperfusion. Thus, even after apparently successful revascularization, muscle ischaemia and infarction may progress[107]. Revascularization also flushes harmful leucocyte products into the systemic circulation. These undoubtedly contribute to multiple organ failure, which may account for up to 20 per cent of postoperative deaths associated with emergency vascular surgery[108]. Patients undergoing aortic aneurysm surgery, both electively and as an emergency for rupture, show evidence of leucocyte activation. Baigrie and colleagues[109] examined plasma levels of IL-1, IL-6 and TNF in 22 patients undergoing elective aneurysm repair and found that a brief rise in IL-1 concentration preceded an IL-6 response. Three patients who developed postoperative complications showed significantly higher IL-6 responses. IL-6 levels also correlated with acute physiology scores. This study was unable to show a rise in TNF concentration. The authors postulated that IL-6 levels might prove to be a useful predictor of outcome. In a further study[110] the same authors reported increased levels of IL-6 in portal venous blood but found no clear relationship with portal endotoxaemia. This led them to conclude that the portal circulation draining the colon was a major source of the previously observed systemic rise in IL-6 levels. Elective aortic aneurysm repair is associated with an increase in urinary albumin excretion, indicating a generalized increase in vascular permeability. This rise correlated with the development of pulmonary complications[111]. Aortic surgery is also associated with a rise in systemic thromboxane levels. In a series of 38 patients randomized to receive mannitol or saline before cross-clamping, mannitol reduced neutrophil activation (as measured by free radical production), thromboxane production and postoperative rises in creatinine level and pulmonary shunting[112]. Soong and colleagues[113] found that diarrhoea after aneurysm surgery was associated with low intramucosal pH and high serum endotoxin and TNF levels.

Complex acquired coagulopathies also develop following aortic aneurysm rupture, and thrombocytopenia and a raised prothrombin ratio are associated with a greatly increased postoperative mortality rate[114]. Although the basis of this coagulopathy is poorly understood, the release of leucocytes and leucocyte products from ischaemic tissue is strongly implicated[115]. Clotting is only one of several cascades that proceed through the sequential activation of proteolytic enzymes on leucocyte, and particularly monocyte, membranes[116]. With respect to ruptured aortic aneurysm it is postulated[117] that shock may cause activation of monocytes and the release of IL-1, IL-8 and TNF. This in turn leads to the recruitment and activation of neutrophils and endothelial cells[118]. Activated endothelial cells and leucocytes inappropriately activate circulating platelets and clotting cascades to produce disseminated intravascular coagulation[119]. Neutrophil elastase increases the adhesivity and procoagulant activity of endothelial cells and activates complement. The end result is local tissue destruction, coagulopathy and multiple organ failure (*Figure 3*).

Therapeutic intervention

Peripheral arterial disease and chronic venous insufficiency appear, at least superficially, to be very different. However, in terms of the pathological processes leading to tissue damage they clearly share important features. In both conditions primary macrocirculatory disease results in secondary microcirculatory changes that cause leucocyte and endothelial cell activation. Furthermore, in both diseases reperfusion may be as damaging as ischaemia. The effects of both arterial and venous disease may therefore be successfully ameliorated by normalizing leucocyte and endothelial cell function. Several drugs in current use, such as heparin, warfarin and aspirin, may indirectly affect leucocyte function, but this is not perceived as their main therapeutic action[120]. A number of newer therapies aimed specifically at modulating leucocyte–endothelial interaction are now being evaluated[121–124].

Inhibition of leucocyte adhesion

Monoclonal antibodies to adhesion molecules have been used to prevent neutrophil adhesion and so attenuate ischaemia–

reperfusion injury[125]. The antibody 60.3 directed against the human neutrophil adhesion molecule CD18 reduces neutrophil-mediated endothelial cell damage *in vitro* and *in vivo*. Antibody treatment reduces the incidence of multiple organ damage and improves survival in animal models of ischaemia–reperfusion injury including primates subjected to haemorrhagic shock followed by fluid resuscitation[126], a situation akin to ruptured aortic aneurysm. Perhaps surprisingly, treatment does not appear to increase the mortality rate from septic shock in animals with abdominal sepsis[127]. Elastase inhibitors and selective platelet depletion also reduce neutrophil adhesion and accumulation in ischaemic tissue[128,129].

Antiplatelet strategies

The most well known antiplatelet strategy modifies prostanoid synthesis such that prostacyclin release is augmented while thromboxane/leukotriene synthesis is relatively reduced[130]. This is discussed separately below. Another possibility is to use PAF antagonists[131]. PAF levels are raised in ischaemia of many organs including the brain, liver, mesentery, heart and lung. PAF increases neutrophil chemotaxis, adhesion to endothelial cells, and elastase and free radical production[132–135]. PAF antagonists protect animals from the consequences of shock caused by haemorrhage, septicaemia, burns and visceral ischaemia[136].

Secondary messenger modulation

Platelet and leucocyte–endothelial cell interactions may also be affected by manipulating secondary messenger systems. Protein kinase C (PKC) mediates the effects of several ligands on platelets and endothelium and, as the enzyme exists as a number of isozymes, it may be possible to develop selective inhibitors[137]. The activation of endothelial cells by IL-1 and TNF is mediated by PKC, and a specific inhibitor (H-7) reduced the adherence of polymorphonuclear leucocytes to IL-1- and TNF-stimulated human endothelial cells *in vitro*[138]. Adenosine 3′,5′-cyclic monophosphate (cAMP)-dependent protein kinase is also implicated in the control of adhesion molecule expression and its different isoforms are selectively inhibited and stimulated by various cAMP analogues[139,140].

Prostaglandin analogues

Protaglandin analogues possess a number of actions that would seem beneficial in arterial disease. They exert an antiatherosclerotic action through inhibiting smooth muscle and fibroblast proliferation by suppressing the release of growth factors from endothelial cells and leucocytes[141,142]. They possess profibrinolytic and antithrombotic properties, inhibit intimal cholesterol accumulation in the vascular wall[143] and inhibit neutrophil degranulation, free radical production, chemotaxis, adhesion and neutrophil-dependent thrombosis and platelet activation[144–150]. They also exert a direct cytoprotective effect on endothelial cells by reducing calcium influx, oxidative metabolism and the production of toxic metabolites[151], and by preventing the hypoxia-induced loss of endothelial defences such as reduced EDRF and prostacyclin production[152–154]. In summary, prostacyclin analogues may preserve function in the hypoxic microvasculature through limiting leucocyte activation and endothelial cell dysfunction. In a multicentre randomized double-blind controlled trial, the prostaglandin (PG)I_2 analogue iloprost was found to be significantly better than placebo in terms of the requirement for amputation in 151 patients with ischaemic ulcers and gangrene[155]. Similar trials have reported reduced amputation and mortality rates following treatment with iloprost in patients with critical limb ischaemia[156,157]. Prostanoids may also be of value in other clinical settings. For example, PGE_1 may attenuate the abnormalities seen in lung function after aortic surgery[158], and iloprost may improve graft flow following femorodistal bypass[159,160] and be of value in chemotherapy-induced digital ischaemia[161]. Another way of modulating prostanoid levels is through the use of thromboxane synthetase and lipo-oxygenase inhibitors, and thromboxane and leukotriene antagonists[162]. The thromboxane synthetase inhibitor OKY-046 and the lipo-oxygenase inhibitor diethylcarbamazine were found to reduce white cell activation and infarct size in an animal model of limb ischaemia[11,163].

Endothelium-derived relaxing factor

Treatment with L-arginine, the substrate for nitric oxide synthetase in the production of EDRF, has been reported to correct endothelial cell dysfunction in an animal model of atherosclerosis[164] and in patients[165]. In addition, as EDRF is inactivated by free radicals, antioxidant agents may also improve endothelial cell function by increasing EDRF activity[166]. Nitric oxide, which is thought to be (or at least very closely related to) EDRF, has recently been reported to be of clinical benefit in patients with ARDS[167]. It is postulated that nitric oxide may act not only through its vasodilator action but also by inhibiting the neutrophil-, platelet- and cytokine-dependent 'systemic inflammatory response syndrome' that accompanies a range of severe illnesses including ischaemia[168].

Free radical inhibition

Various methods of limiting free radical injury have been evaluated including control of reperfusion flow and oxygenation, use of free radical scavengers and intervention aimed at preventing, or at least limiting, leucocyte and/or endothelial cell activation[169] (*Table 1*). In a recent animal study haemofiltration using a combination of mannitol, superoxide dismutase, methylprednisolone, heparin and α-tocopherol (a free radical scavenger) was found to protect against reperfusion renal failure and muscle damage after ligation of the aorta and inferior vena cava[170]. In another study the radical scavenger oxpentifylline was found to be significantly better than placebo in reducing recovery time, as measured by transcutaneous oxygen tension, in a group of 30 patients with intermittent claudication. These effects were also associated with a significant improvement in leucocyte filterability, leucocyte pseudopodia formation and serum oxidant activity[176]. Free radical inhibition may also be of value in preventing the systemic manifestations of ischaemia. Allopurinol inhibited arteriolar disruption in a mesenteric ischaemia–reperfusion model[177] and mannitol has been shown to be effective in limiting the neutrophil activation that follows aortic surgery. This is thought to result from inhibition of thromboxane synthesis initiated by free radicals released from ischaemic tissue[180]. Allopurinol and another scavenger, dimethyl sulphoxide, may also be of value in the treatment of venous ulceration. In a double-blind controlled study, use of these drugs with compression bandaging healed over 93 per cent of ulcers at 3 months compared with only 70 per cent of ulcers treated with compression therapy alone[73].

Oxpentifylline

Oxpentifylline, a drug that has been advocated for the treatment of both arterial and venous ulcer disease, appears to modulate

Table 1 *Methods of preventing ischaemia–reperfusion injury*

Control of reperfusion flow and oxygenation[170]
Free radical scavengers (mannitol, prednisolone, heparin, superoxide dismutase, vitamin E)[171,172]
Xanthine oxidase inhibitors (allopurinol)[73]
Haemofiltration[172]
Adhesion molecule blockade by specific antibodies[173]
Leucocyte depletion[174,175]
Inhibition of leucocyte activation[122,124]
Inhibition of free radical production[176,177]
Inhibition of leucocyte–endothelial cell adhesion[126,148]
Inhibition of thromboxane production[162,178]
Prostacyclin infusion[11,179]
Complement activation inhibition by cobra venom[54]

Table 2 *Actions of oxpentifylline*

Increases mononuclear phagocyte and granulocyte filterability through artificial membranes[185]
Reduces leucocyte–endothelial cell adhesion[186]
Inhibits thrombin- and complement-induced leucocyte adherence to endothelial cells[187]
Inhibits free radical production[187]
Inhibits phagocytosis[188]
Inhibits the ability of platelet-activating factor to activate neutrophils[189]
Inhibits the activating and adhesion-promoting effects of cytokines (tumour necrosis factor, interleukin 2)[184,190] on leucocytes *in vitro* and *in vivo*
Inhibits endotoxin-induced pulmonary neutrophil sequestration[191]
Inhibits platelet aggregation through changes in adenosine 3′,5′-cyclic monophosphate levels, reduction in thromboxane and increase in prostacyclin synthesis[192]
Increases red blood cell deformability[192]
Decreases blood fibrinogen level, and whole blood and plasma viscosity[192]
Inhibits platelet adhesion to vascular endothelium[193]
Reduces endothelial permeability[193]
Increases fibrinolysis[194]

leucocyte and endothelial cell function through a number of different mechanisms[181–184] (*Table 2*). Several early studies indicated that oxpentifylline can improve ankle artery blood pressure, walking distance, rest pain, and muscle blood flow and oxygenation in patients with arterial occlusive disease. However, it has been argued that many of these studies are small and poorly designed, and oxpentifylline is not widely used in the UK for the treatment of peripheral arterial disease. Nevertheless, in a recent double-blind multicentre trial of 150 patients, the drug was found to be statistically superior to placebo[195], especially in those with an ankle:brachial pressure index below 0·8. Oxpentifylline has also been shown to promote the healing of venous leg ulcers in a multicentre double-blind placebo-controlled study of 80 patients, confirming the results of earlier uncontrolled trials[196]. The effects of this agent on white cell activation, deformability and endothelial adhesion appear, therefore, to be of benefit in arterial and venous disease, supporting the contention that similar pathological processes are involved in both.

In addition to its local effects, oxpentifylline may attenuate the neutrophil-mediated systemic response to ischaemia–reperfusion injury. In a double-blind placebo-controlled trial oxpentifylline was found to reduce albumin excretion after exercise significantly relative to creatinine in a group of 20 patients with intermittent claudication[197]. This led the authors to conclude that the deleterious systemic effects of localized ischaemia could be attenuated by the drug. Oxpentifylline also preserves intestinal microvascular flow and may protect against ARDS following shock[184,198]. These effects are at least partly mediated through inhibition of TNF and IL-2 and by optimizing flow dynamics between leucocytes and endothelial cells in the microcirculation. For example, oxpentifylline suppresses TNF gene transcription in acute endotoxaemia[199].

Cytokine modulation

Cytokines represent a potential target for intervention through either the development of specific receptor antagonists or the interruption of secondary messenger pathways[200,201]. In the case of IL-1, a naturally occurring specific receptor antagonist has been discovered[202]. Recombinant IL-1 receptor antagonist is currently being evaluated in the treatment of a range of medical conditions including septic shock[42,203]. With respect to vascular disease IL-1 receptor antagonist inhibits neutrophil accumulation, endothelial–leucocyte adhesion, leucocyte cytokine production and release of free radicals[204,205]. There is also evidence that diets rich in fish oils decrease IL-1 production by leucocytes and inhibit the development of atherosclerosis[206]. IL-1 could also be inhibited by neutralizing antibodies, by preventing synthesis of its active form[207] and through the development of soluble IL-1 receptors[208]. A naturally occurring soluble form of the receptor has been found in body fluids although its biological function is unknown[209]. Another approach might be through the use of inhibitory cytokines that downregulate the production of proinflammatory cytokines[210] such as IL-1 and TNF. For example, IL-10 inhibits antigen presentation and cytokine (IL-1, IL-6, IL-8, TNF, CSF) production by cells of the macrophage–monocyte lineage. IL-10 also inhibits adhesion and the production of oxygen metabolites but upregulates expression of IL-1 receptor antagonist. IL-10 protects mice from death caused by endotoxaemia[211].

Aprotinin

The clinical importance of coagulopathy and the role played by activated leucocytes after aortic aneurysm rupture have already been discussed. Aprotinin is now widely used to reduce the bleeding associated with cardiopulmonary bypass. The drug also reduces blood loss during and after elective aortoiliac surgery[212]. Aprotinin is a protease inhibitor and is thought to act on fibrinolysis, kallikrein and complement activation[213]. There is also evidence that the drug may affect neutrophil function after major vascular surgery. Lord and colleagues[214] found that perioperative aprotinin therapy maintained significantly better postoperative white cell function in terms of morphology, unstimulated nitroblue tetrazolium reduction and chemotaxis. Blood loss was also significantly decreased. The present authors are currently involved in a trial to determine whether perioperative aprotinin treatment can reduce blood loss, prevent coagulopathy and ultimately improve survival in patients presenting with ruptured aortic aneurysm.

Conclusions

The reason for conducting primary scientific research into vascular, and indeed all, disease is the hope that a better understanding of basic pathological processes will result in novel methods of treatment. The ultimate aim must be the development of systemic treatments specifically aimed at key points in these processes that will prevent or at least limit tissue damage. At present, understanding of leucocyte, platelet and endothelial cell biology is in its infancy but potential targets for such specific intervention are already becoming apparent. It may be that such intervention will enable control of many aspects of both arterial and venous disease.

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Review

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Cocaine 'body packers'

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Intracorporeal drug smuggling, particularly of cocaine, is increasing. The so-called 'body packers' present a difficult clinical problem, particularly as no coherent management policy has been formulated. The various methods of diagnosis and the treatment options available are presented and discussed.

'Body packers' or 'mules' are drug traffickers who attempt to smuggle drugs, mainly cocaine or heroin, by intracorporeal concealment. Packages containing the drug are usually swallowed or inserted into the rectum to be retrieved after the trafficker has cleared customs. 'Body stuffers' or 'quick swallowers' are drug dealers who ingest packages or vials of drugs when suddenly confronted by the authorities.

Although the gastrointestinal tract is the preferred site for intracorporeal drug concealment, almost no orifice has been overlooked. The insertion of illicit drugs into the vagina[1,2] and even the ear[3,4] has been described. While the majority of body packers do not require medical attention, the detection of body packing is important because the practice has resulted in bowel obstruction[5,6] and acute drug toxicity[7–12]. Fatalities are particularly common following cocaine intoxication[7,9,10]. Since the first reports[5,13–15] of gastrointestinal drug smuggling in the 1970s, most reported cases have been from the United States or continental Europe. However, this technique of smuggling is being used with increasing frequency and body packers are becoming an increasing problem in the UK[16,17]. The majority of patients have been apprehended at international airports by customs officials and are then transferred to hospital only after developing complications. Some body packers become frightened and present to an accident and emergency department directly. The greatest management problems are caused by cocaine ingestors.

Cocaine

Cocaine (methylbenzoylecgonine) is an alkaloid, prepared from the leaves of the *Erthroxylon* plant[18,19], that is currently marketed in the form of crystals, granules or a white powder. The systemic effects of cocaine are probably mediated by alterations in synaptic transmission; it blocks the presynaptic re-uptake of the neurotransmitters noradrenaline and dopamine, which produces an excess of transmitter at the postsynaptic receptor sites. Sympathetic activation by this mechanism produces vasoconstriction, an acute rise in arterial pressure, tachycardia and a predisposition to arrhythmia, seizures, hyperglycaemia and hyperthermia[19,20]. For cocaine, the median lethal dose fatal to 50 per cent of human test subjects is said to be 500 mg after oral ingestion[21], but the fatal dose[19] can be as low as 20 mg. A relatively rapid increase in blood level may be as important in determining a fatal reaction as the peak blood concentration[10,22]. This may be of particular relevance in the context of the body packer.

Cocaine packages

The number of packages recorded as swallowed[6,23,24] ranges from 15 to over 200, each package containing 3–15 g cocaine[6,11,23,24]. The packages are constructed in a variety of ways (*Figure 1*), but generally consist of cocaine powder wrapped in cellophane and three or four layers of latex tied with a non-absorbable surgical ligature. McCarron and Wood[23] classified packages into three types (*Table 1*). While rupture of a single package can lead to massive fatal cocaine poisoning[9], the packages do not have to break open to cause death. The wrapping may serve as a semipermeable membrane, allowing fluid from the gastrointestinal tract to permeate the wall of the package; cocaine hydrochloride, being a salt, dissolves and diffuses out[1]. It has been estimated that 25 per cent of packages are highly susceptible to breakage or leakage[23].

Clinical presentation

There is a broad spectrum of presentation, from the entirely asymptomatic but anxious body packer who arrives at an accident and emergency department, to the packer with acute cocaine intoxication. The typical body packer is a young man recently arrived from South America[7,8,14,15]. Predictably, a good history is not always available[23] but, if the patient is confronted with the fact that cocaine metabolites have been positively identified in the urine, in the authors' experience they will often admit to how many packages they have swallowed. In asymptomatic patients initial examination is also often unhelpful[11]. Most body packers are not cocaine users

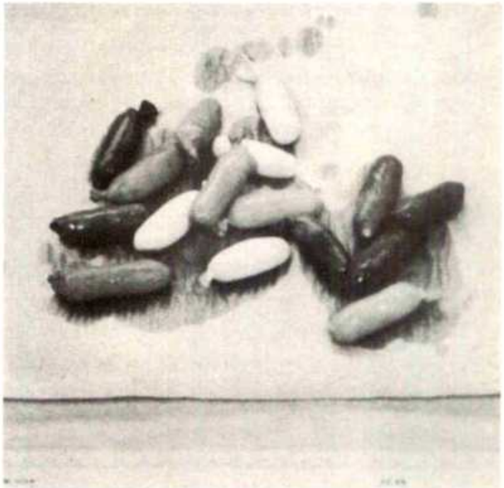

Figure 1 *Cocaine packages. In this case toy balloons were used as the packaging material*

Table 1 *Classification of cocaine packages*[23]

Characteristic	Type 1	Type 2	Type 3
Cocaine	Loose powder	Matted powder	Paste
Packaging	Condoms, toy balloons or fingers of latex gloves	Tubular latex	Aluminium foil and tubular latex
No. of layers	2–4	5–7	3–5
Risk	Susceptible to breakage	Resistant to breakage	Resistant to breakage

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themselves and features of intravenous drug abuse or chronic cocaine abuse are absent[11]. Small mobile packages may occasionally be felt on abdominal or rectal examination.

Anticholinergic drugs

The body packer may have taken anticholinergic agents, for example up to 20 tablets of Lomotil (atropine sulphate 0·025 mg, diphenoxylate hydrochloride 2·5 mg; Gold Cross Pharmaceuticals, High Wycombe, UK) per day, to slow the transit time of the ingested packages during a long flight from South America[23–25]. Symptoms such as a dry mouth, mydriasis and accommodation difficulties may therefore be evident.

Obstruction

Obstruction may be the first presenting feature[5,6]. Obturation obstruction of the bowel probably occurs when the cocaine-filled packages become entangled[5]. The most common sites are the pylorus, ileocaecal valve and splenic flexure[6]. Previous surgery may increase the likelihood of obstruction if adhesions have led to extrinsic areas of narrowing.

Acute cocaine intoxication

Signs and symptoms of acute cocaine intoxication should always be sought, although they are often absent when the patient first presents[23]. Classically, intoxication is manifested by agitation, diaphoresis, tachycardia, palpitations, hypertension, hyperthermia, disorientation, hallucinations and paranoid behaviour[20]. After the massive doses that may be absorbed when a package breaks, the patient may develop arrhythmia, seizures and metabolic and respiratory acidosis. Such cases are usually fatal[1,7,9,10,26,27].

Investigations

As the initial history and examination are often not helpful the diagnosis is established largely by a combination of urine analysis and radiology.

Urine analysis

Detection of opiates and benzoylecgonine, the major metabolite of cocaine, in the urine is possible by enzyme immunoassay[24,28]; a result can be available[28] within 10 min. There is a good correlation between the presence of drugs in the urine and cocaine packages in the body[24,29]. Gherardi *et al.*[29] tested the urine of 50 cocaine body packers and detected benzoylecgonine in 49. The sensitivity of the benzoylecgonine test is greatest (up to 97 per cent) on the first day of admission to hospital, but the accuracy of the test progressively decreases as the ingested cocaine packages are spontaneously eliminated[24]. The test is often positive, even if the packages have remained intact. This may be because some packages are semipermeable or because contamination of the outside of the packages occurred when they were made[24,28].

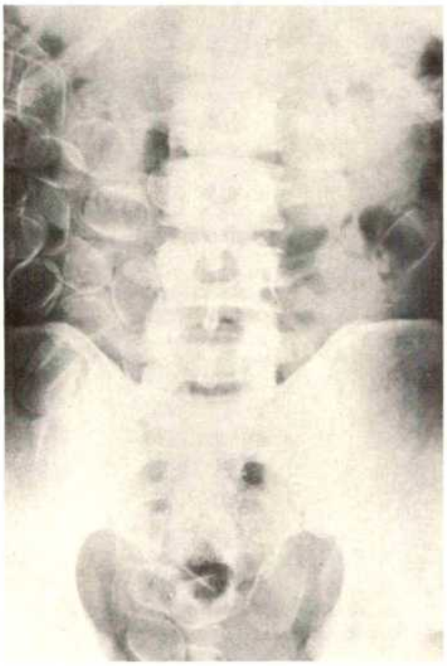

Figure 2 *Plain abdominal radiograph showing cocaine packages in the bowel*

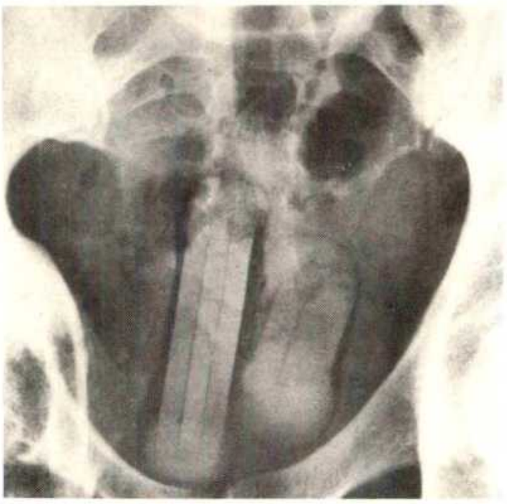

Figure 3 *Plain abdominal radiograph showing cocaine packages inserted in the rectum*

Radiology

The usefulness of plain abdominal radiography in the diagnosis of cocaine body packers is well established[6,23,25,30–32] (*Figures 2* and *3*). The drug may be detected in the gastrointestinal tract as a consequence of the way in which it is packaged. Air trapped between layers of condoms may be seen; this is the 'double condom' sign first described by Pinsky *et al.*[33]. Air trapped in the outer package at the end where the knot has been tied may be seen as a 'rosette' shape[23,31]. Radiographs are taken not only to establish diagnosis but also to determine the type of package and its position in the gastrointestinal tract. Packages are easier to identify in the stomach as the gastric air bubble acts as a contrast agent; however, the most common location in which they are identified is the ascending colon[31]. False-negative results can occur, but plain abdominal radiography will lead to a correct diagnosis in 83–92 per cent of cases[6,31].

Contrast study of the bowel has been variably reported as unreliable or useful[11,23,29,30,34]. Those who advocate its use point out that, as water-soluble contrast medium is osmotically active, it accelerates the spontaneous elimination of packages by acting as a purgative. Ultrasonography has not been shown to increase significantly the detection rate of packages[35].

Other investigations

Routine blood investigations are invariably taken, although they do not often contribute to establishing a diagnosis. Arterial blood gas analysis may confirm acidosis if cocaine intoxication is present[26] and blood should be taken for assay of serum cocaine levels[7,8]. Cardiac events related to cocaine intoxication are well described and electrocardiography should be performed[20,36–39].

Management

The aim of any form of management is to attempt to prevent death or complications from acute cocaine poisoning or obstruction. The retrieval of packages for legal purposes is not an indication for intervention. Management depends on the type of package ingested, their location in the gastrointestinal tract, the length of time elapsed since ingestion and, most importantly, the physical findings, in particular the presence or absence of cocaine poisoning or obstruction.

Surgery

The risk of rupture of a package has not been determined in any large series, but surgical removal of all packages from all body packers is almost certainly an invasive over-reaction. On the other hand, most authors agree that obstruction and evidence that the ingested packages are disintegrating are both absolute indications for operation[5,6,11,16,23,25,31,34]. If the packages are poorly constructed or of the type most likely to leak (McCarron–Wood[23] type 1), surgical intervention should also be considered. The type of package may be determined radiologically but analysis of one that has already been passed is, of course, more reliable. The risk of disintegration of packages is increased if they have been present in the gastrointestinal tract for a prolonged period. Failure to eliminate the packages is, therefore, a relative indication for operation[1].

At laparotomy a single enterotomy is usually sufficient as the packages can be 'milked' to the enterotomy site and evacuated manually. Occasionally more than one enterotomy is required[5,25].

Bowel ischaemia has been reported secondary to ingestion of cocaine[40,41], although not yet in a body packer. Although at present this remains only as a theoretical risk, with the increasing frequency of intracorporeal cocaine concealment it should be considered as a possibility.

Endoscopy

Upper gastrointestinal endoscopy has been used both to confirm the diagnosis and to remove packages[34]. However, packages may be damaged as they are snared and so this technique is not recommended[7,11,23,26].

Induced emesis and purgation

Induced emesis is of most use in quick swallowers. The hastily ingested packages are particularly susceptible to leakage and quick evacuation of the stomach contents is therefore the aim[11,12,27,42–44]; 15 ml ipecacuanha after drinking 200 ml water is recommended, and a second dose may be given[42]. The present authors have found the same regimen useful in retrieving packages from the stomach in body packers.

Purgation will be successful in the majority of patients without obstruction[6,11,23,30]. Caruana *et al.*[6] describe a study of 50 cocaine body packers: six chose elective surgery, three had emergency surgery for obstruction and 41 were successfully managed by purgation. A clear liquid diet was given and the patients commenced on mineral oil 30 ml four times a day. In this study none of the patients presented with or developed signs or symptoms of cocaine intoxication[6]. Similar results have been obtained with a regimen of 100 ml oral paraffin twice daily[11]. Enemas should be avoided, as packages within the rectum may be damaged by insertion of the enema nozzle[26]. A single instance of whole bowel irrigation has been described[34] in which all packages were successfully eliminated without complication. The patient was required to drink 20 litres of polyethylene glycol electrolyte lavage solution.

Management of cocaine intoxication

Survival is rare after massive cocaine poisoning[7,9,10,20,26]. Most deaths are attributed to generalized convulsions, cardiac arrhythmia or respiratory failure, but the precise sequence of events leading to death is poorly understood[20]. Medical management largely involves treating complications as they arise. The patient developing signs and symptoms of cocaine intoxication should be transferred to an intensive care unit for monitoring. Propranolol 1 mg per min intravenously may specifically antagonize the sympathomimetic effects of cocaine[45–47]. Pretreatment with diazepam 2·5–5·0 mg or high-dose chlorpromazine has been used effectively to prevent seizures and, in addition, it has been suggested[26,48,49] that this drug will counteract the sympathomimetic effects of cocaine on the heart. Nitrendipine may also be an effective antagonist to the cardiotoxic effects of cocaine[50]. Hyperthermia may not respond to standard evaporative cooling methods and in such circumstances dantrolene sodium 1 mg/kg intravenously over 10–15 min has been used, albeit with variable success[17,51–53]. Once the patient has been stabilized, any remaining packages are also at risk of disintegration and should be removed surgically.

Conclusions

Body packing should be considered as a diagnosis in any international traveller who presents with signs or symptoms compatible with cocaine intoxication. For asymptomatic patients, a trial of conservative management will lead to the uncomplicated elimination of all packages in the majority. However, rupture of a single package can lead to death and so early surgical intervention is probably the safest policy if there is evidence that the packages are disintegrating or are likely to do so. Obstruction or acute cocaine intoxication are absolute indications for operation once the patient has been stabilized.

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Digest

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The July to September issues of Surgery Today (The Japanese Journal of Surgery) *form the basis for this quarter's digest by that journal's Editor-in-Chief, Professor Yoshio Mishima.*

Oncology

Kase *et al.*[1] investigated the modulating effect of folinic acid (leucovorin) on the antitumour action of 5-fluorouracil (5-FU) against C-1 human colonic carcinoma cells *in vitro* and Co-4 human colonic cancer xenografts in nude mice. The modulating effect of folinic acid on 5-FU was optimal at a concentration of 40–80 μg/ml *in vitro* as determined by a colorimetric 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay. An optimal dose of 200 mg/kg was observed in the nude mouse system. The modulating effect of folinic acid increased according to the extent of thymidylate synthetase inhibition *in vivo*. Since the pharmacodynamics of folinic acid in nude mice given the drug at 200 mg/kg were similar to those in patients treated at a dose of 100 mg/m^2, this method of administration was thought to be adequate for modulating the antitumour activity of 5-FU in clinical practice.

Oka *et al.*[2] studied the natural killer (NK) activity of peripheral blood mononuclear cells and serum immunosuppressive acidic protein (IAP) levels in patients with oesophageal or gastric cancer before and after surgery. Patients with stage IV oesophageal or gastric cancer had significantly lower NK cell activity (mean(s.d.) 39·5(14·8) and 37·0(11·6) per cent respectively) and higher serum IAP levels (mean(s.d.) 778(264) and 633(156) μg/ml respectively) than corresponding controls (50·0(5·6) per cent and 375(26) μg/ml). Patients with oesophageal or gastric cancer who underwent curative resection had high NK cell activity (mean(s.d.) 54·8(11·6) and 54·8(8·0) per cent respectively) and low IAP levels (mean(s.d.) 471(116) and 490(42) μg/ml) compared with those undergoing palliative resection, and this effect was seen 1 month after surgery. Mononuclear cells in the regional lymph nodes and tumour specimens showed significantly lower NK cell activity than those in the peripheral blood and spleen. Thus, NK cell activity and IAP level reflected the immunocompetence, clinical course and surgical curability of these patients. NK cells appeared not to have significant antitumour activity in the regional lymph nodes or in the tumour itself, although they were still active in the peripheral blood.

Toge *et al.*[3] investigated the role of lymphocyte surface binding sites for wheat germ agglutinin (WGA) in the negative regulation of disease in patients with malignancy. The number of WGA binding sites on the surface of each lymphocyte ranged from 10^7 to 10^8. Fluorescein isothiocyanate-conjugated WGA bound to the majority of peripheral blood lymphocytes with two peaks of fluorescent intensity (dim and bright). The increase in the proportion of lymphocytes with bright fluorescence ('WGA-bright' lymphocytes) correlated significantly with the number of WGA binding sites. The suppression of lymphocyte proliferation mediated by purified soluble suppressor factor correlated significantly with an increase in the size of the WGA-bright lymphocyte population ($P < 0·05$). A significantly greater number of WGA-bright peripheral blood lymphocytes was found in patients with oesophageal, gastric, breast and colonic cancer than in those with benign disease or healthy controls. An increase in the number of WGA-bright lymphocytes was found in subsets expressing the antigens CD8 dimly or CD16. The number of WGA binding sites may therefore increase on the surface of effector cells such as NK and CD8-positive killer T cells in patients with cancer, triggering the negative regulation mediated by soluble suppressor factor.

Gastric cancer

Ichikura *et al.*[4] studied 318 patients undergoing curative resection for gastric cancer, 168 with and 150 without prognostic serosal invasion, to determine the prognostic importance of clinicopathological factors and identify which patients were at high risk of recurrence. Multivariate analysis of survival using a Cox proportional hazards model was carried out to determine important prognostic factors. In patients with prognostic serosal invasion these emerged as lymph node involvement, the classification of gross tumour appearance, macroscopic serosal invasion and interstitial connective tissue. Lymph node involvement, macroscopic serosal invasion and venous invasion were important factors in patients without prognostic serosal invasion. A risk score for recurrence was derived based on the results of further multivariate analysis (Hayashi's Quantification Analysis II)[5], in which recurrence was chosen as an objective variable with the prognostic factors mentioned as explanatory variables. Some 84 per cent of patients with prognostic serosal invasion and a score of 0 or higher and 83 per cent of those without such invasion and a score of +6 or more developed recurrence. This score may thus be useful for identifying patients at high risk of recurrence, who should receive intensive chemotherapy after curative resection.

Breast cancer

Narita *et al.*[6] investigated the utility of serum levels of procollagen type III N peptide and the type IV collagen 7S domain as markers of recurrence and metastasis in 199 patients with breast cancer. Serum levels of N peptide and the 7S domain were significantly higher in patients with postoperative recurrence, with 76·9 per cent of N peptide-positive patients with cancer and 68·0 per cent of those with malignancy positive for the 7S domain having metastases in the bone and/or liver. Furthermore, 66·7 per cent of all patients with metastases in the bone and/or liver were positive for N peptide and 75·6 per cent for the 7S domain. Patients with liver metastases were either N peptide or 7S positive and levels were higher than those in patients with bone secondaries. These findings suggest that serum levels of both collagen peptides are useful markers of recurrent and metastatic breast cancer, especially in the bone and/or liver.

Liver transplantation

An animal model of split liver transplantation using pigs is described by Tanaka *et al.*[7]. The donor liver was divided into two grafts, the right graft consisting of the right medial and lateral segments with the caudate lobe, the left of the left lateral and medial segments. To make implantation easier a distal part of the donor inferior vena cava (IVC) was isolated and attached to the left graft with anastomosis between the orifice of the renal vein and the graft hepatic vein. The left graft thereby contained a newly constructed retrohepatic IVC for anastomosis to the recipient. During the anhepatic phase, no conventional bypass procedure was used, but abdominal aortic clamping in combination with general hypothermia was employed. Ten pigs were used as donors and 20 liver transplants performed; no immunosuppressive drugs were given. Ten of the 20 recipients survived more than 2 days, the mean survival time being 4·7

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(range 2–14) days. The survival time of animals receiving left grafts was much longer than that of those given right grafts, although no technical problems such as graft kinking or hepatic vein occlusion were encountered in either group. This is the first report of split liver transplantation in animals. The advantages of the infrahepatic IVC graft include stability of the graft and safe hepatectomy. This model will therefore be useful for the experimental study of split liver transplantation and the method may be employed clinically in the future.

Endoscopic surgery

Lifting of the abdominal wall is a means of producing space between the anterior abdominal wall and the intra-abdominal organs during laparoscopic surgery. Hashimoto *et al.*[8] devised a hanger lifting procedure for the anterior abdominal wall to avoid complications and reduce the costs related to pneumoperitoneum. Fifty patients underwent laparoscopic cholecystectomy with this abdominal wall-lifting procedure. Initially cholecystectomy by pneumoperitoneum was used but eventually the insufflator was discarded. There was no incidence of conversion to pneumoperitoneum and a relatively good operative view was achieved enabling trouble-free laparoscopic cholecystectomy.

Coronary artery bypass

Histopathological and biochemical studies were conducted by Kobayashi *et al.*[9] on the severity of arteriosclerosis of the internal mammary artery (IMA), as used for coronary artery bypass grafting. Twenty-six bilateral IMAs and 13 left anterior descending coronary arteries (LADs) obtained in full length from 13 autopsies were studied. In no case had the patient died from atherosclerotic heart disease. The ratio of the thickness of the intima to that of the media was used as an index of atherosclerosis. IMAs and LADs were classified as grades I–IV according to this index. The atherosclerosis index of the IMAs was approximately one-tenth that of the LADs ($P < 0{\cdot}01$). Most IMAs showed a low atherosclerosis grade, with no variation along the length and a low index in all segments. No difference was found between right and left IMAs. Biochemical studies were carried out on 12 IMAs and 11 LADs obtained from 12 different unselected autopsies. The lipid content of the vascular wall was determined to evaluate the severity of atherosclerosis. The mean(s.d.) lipid levels of the IMA and LAD for total cholesterol were 5·5(1·8) and 17·8(13·6) μg per mg wet weight respectively ($P < 0{\cdot}05$), for triglyceride 90·4(90·3) and 114·4(117·2) μg/mg (P not significant) and for phospholipid 7·4(3·9) and 11·2(3·9) μg/mg ($P < 0{\cdot}05$). The authors concluded that atherosclerosis of the IMA is mild compared with that of the LAD in the same individual.

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Digests

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Br. J. Surg. 1993, Vol. 80, December, 1519–1521

For this quarter's digest, Professor Christian Herfarth and Dr Thomas Lehnert have selected from the July to September issues of Der Chirurg. *A reciprocal digest of the* BJS *written by Professor John Farndon appears in the German journal.*

Soft tissue sarcoma

In a second series of articles on soft tissue sarcoma, Dosluoglu *et al.*[1] review treatment options for extremity sarcoma with particular emphasis on wide local excision and compartment resection. Wide local excision represents removal of the primary tumour with at least a 2-cm margin of normal tissue. After this procedure high-grade tumours will show a local recurrence rate of up to 50 per cent and therefore require additional chemotherapy or radiotherapy. For low-grade tumours wide local excision appears to be sufficient if all gross tumour is removed and the margins are free from microscopic disease. Compartment resection, in contrast, requires removal of all soft tissue that constitutes the anatomical compartment in which the tumour resides, together with the fascial sheath. Overall results of this treatment are similar to those of extremity amputation, with recurrence rates of 15–20 per cent; compartment resection should be preferred if surgical treatment alone is considered for high-grade sarcoma (for example, radiation-induced sarcoma). Compartment resection may be difficult for tumours located in the groin, popliteal fossa or distal forearm, because there is little surrounding tissue, and preoperative radiochemotherapy with wide local excision may be preferable. Amputation may be necessary for large tumours in these locations. In the thigh, compartment resection may produce specific functional deficits. Potential aids to overcome or ameliorate sequelae of operative treatment are presented. Although functional deficits following compartment resection of the upper extremity are usually more severe than in the lower limb, the remaining function is preferable to that following forearm or forequarter amputation for sarcoma in this location.

Combined treatment of high-grade sarcoma including preoperative, intraoperative or postoperative radiotherapy may result in good local tumour control and preservation of limb function. Wide local excision is the treatment of choice for low-grade sarcoma or small (less than 5 cm) high-grade sarcoma. Postoperative radiotherapy should be considered if margins are less than 2 cm. For high-grade sarcoma and for lesions of more than 5 cm, preoperative intra-arterial chemotherapy is recommended. Tumours larger than 10 cm, fixed lesions or those adjacent to the neuromuscular bundle should be treated by preoperative radiochemotherapy to avoid primary amputation.

Current management of retroperitoneal sarcoma is reviewed by Siewert *et al.*[2], who recommend abdominal computed tomography (CT) with intravenous and enteral contrast media to delineate the tumour and establish its precise anatomical relation to surrounding organs and vessels. CT of the chest is recommended to detect pulmonary metastases. Angiography should be used to detect feeding vessels and local vascular invasion by the tumour. Preoperative needle biopsy guided by ultrasonography or CT was successful in 85 per cent of patients, providing information on cell type and grade. Complete resection of the tumour with clear margins was achieved in approximately 50 per cent of patients. Growth of retroperitoneal sarcoma is not restricted by fascial sheaths and complete removal requires clearing of the quadrant or side on which the lesion is located. This is more often achieved on the left since the hepatoduodenal ligament, the mesenteric root and infiltration of the vena cava may restrict resectability on the right. Multiorgan resection was performed in 34 of 40 patients. Complete tumour removal was possible in half and the perioperative mortality rate was 8 per cent. The median survival of patients with high-grade sarcoma was 12 months. The 5-year survival rate of patients with grade I or II tumours was 56 per cent, whereas no patient with a grade III lesion survived 5 years. Multivariate analysis identified complete removal of macroscopic tumour ($R_{0/1}$ resection) and grade as independent prognostic factors. Over a median follow-up of 38 months the local recurrence rate was 43 per cent. The authors emphasize that on prolonged follow-up approximately 90 per cent of patients who have received R_0 resection will develop local recurrence, while only 30 per cent develop distant metastases within 10 years. No clear advantage of adjuvant radiotherapy or chemotherapy could be determined from a review of the literature.

Large bowel

Several conditions, such as familial adenomatous polyposis (FAP), ulcerative colitis and low rectal cancer, may require total proctocolectomy or excision of the rectum with the need for subsequent restoration of intestinal continuity. Parc and Sales[3] review surgical options to restore continence and report experience with ileoanal pouch construction, coloanal pouch anastomosis and coloanal anastomosis.

Between 1983 and 1991, 156 patients with ulcerative colitis were treated by ileal pouch–anal anastomosis. There were no postoperative deaths. A three-stage procedure was performed in 34 per cent of patients and 28 per cent had postoperative complications. The morbidity rate was lower after three-stage than two-stage operations (17 *versus* 39 per cent). Overall, 10 per cent of patients required reoperation. Nine patients developed a fistula and seven stenosis. Three patients required pouch removal for persistent fistula and in two of these Crohn's disease was diagnosed after operation. During a 6-year period 114 patients with FAP were treated by ileoanal pouch construction. The authors observed no complications or mortality. More than 90 per cent of patients reported full continence and only 15 per cent required dietary restrictions.

Between 1984 and 1990 the same authors performed coloanal J pouch anastomosis in 162 patients with low rectal cancer. The operative mortality rate was 0·6 per cent. All patients had a temporary diverting colostomy. Pelvic sepsis and anastomotic leakage were recorded in 3 per cent of patients and treated conservatively in all. After 1 year, 52 per cent of patients were fully continent and 40 per cent reported minor problems. Some 25 per cent of patients required enemas or suppositories to facilitate bowel movements. The 5-year survival rate was 79 per cent and the recurrence rate 7 per cent.

Defining the exact extent of an anorectal fistula may be difficult on clinical examination or during operation. Hancke *et al.*[4] studied the value of magnetic resonance imaging (MRI) in 17 patients with anorectal fistula in whom clinical examination including proctoscopy and rectoscopy failed to define the extent of the lesion. Nine patients had Crohn's disease and two ulcerative colitis. Nine of the 17 patients had had previous surgery for the fistula. In six of the 17 patients MRI revealed additional tracks that had not been detected by clinical examination and in a further three abscess formation that had been missed by clinical examination was found. Intraoperative findings confirmed the lesions demonstrated by MRI in all but

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one patient. Seven of the nine patients with additional findings on MRI had Crohn's disease. The authors conclude that MRI of the pelvis is an important diagnostic tool to evaluate the extent of complex anorectal fistula.

Hernia repair

Repair of inguinal hernia remains one of the most frequently performed operations. Töns and colleagues[5] conducted a postal survey to determine the status of hernia surgery in Germany. A total of 1656 questionnaires were sent out with a return rate of 66·2 per cent, covering 27 991 operations per year. Just over half of surgeons (54 per cent) indicated that the operation was performed under general anaesthesia, while 40 per cent preferred spinal or epidural anaesthesia. Only 6 per cent of surgeons preferred local anaesthesia. Absorbable sutures were employed by 67 per cent of surgeons and the rest used non-absorbable sutures. Surprisingly, 63 per cent of surgeons advocated subcutaneous placement of the spermatic cord for primary hernia repair irrespective of other technical aspects. When the results of this survey are compared with those of a study conducted 10 years ago the majority of surgeons (54 per cent) now prefer the Shouldice technique for primary and recurrent hernia repair, whereas this was used by only 0·4 per cent in 1982. Only 0·7 per cent of surgeons used any laparoscopic techniques for primary hernia repair. Recurrent inguinal hernia repair was performed laparoscopically in only 1·1 per cent of departments, but 8·6 per cent of surgeons considered the use of mesh as an alternative in the treatment of recurrent herniation. When asked specifically about laparoscopic herniorrhaphy, 87·6 per cent of surgeons documented strong reservations, because this was 'not an established form of treatment' (72 per cent), because conventional repair was considered to be a safer procedure (47 per cent), because it was laborious and expensive (20 per cent) and because it was considered an unphysiological approach or for other reasons (18 per cent). Day surgery for herniorrhaphy was offered by 21 per cent of hospitals and the average stay after repair was 8 days for primary and 10 days for recurrent inguinal hernia.

Vascular surgery

In a prospective randomized trial Bernert and Balzer[6] tested various bifurcation grafts inserted for aortoiliac occlusive or aneurysmal disease. In all, 100 patients were randomized to four groups receiving Dacron (Du Pont, Wilmington, Delaware, USA) prostheses with or without velour and with or without gelatin coating. The operations were performed in 1983 and 1984. Intraoperative blood loss was lowest in patients receiving a gelatin-coated velour prosthesis (878 ml), but the differences between groups were not significant. Ten patients died after operation; the cause of death was myocardial failure in all ten. No patient had evidence of prosthesis infection or perigraft reaction in the postoperative period. Thirteen late deaths were unrelated to the operation or graft and 23 patients refused follow-up examination. Long-term follow-up results after 5·5 years were available for 54 patients, who were examined clinically and by ultrasonography. The latter revealed that 87 per cent of prostheses had increased in diameter by a mean of 17·3 per cent. No significant differences were established for different graft materials. The late amputation rate was 4 per cent and unrelated to the material used. The cumulative primary patency rate(s.e.) was 83(9) per cent at 72 months. The authors concluded that only the highly subjective criterion of ease of intraoperative handling conferred some advantage to the velour prosthesis. No advantage of gelatin coating could be demonstrated.

Oesophageal carcinoma

Cancer of the oesophagus remains a major challenge to all surgeons of the alimentary tract. Nürnberger and colleagues[7] report experience with this disease. Between January 1988 and December 1991, 122 patients with squamous cell carcinoma of the oesophagus were evaluated prospectively. The primary resectability rate was 52 per cent (64 patients). Twenty-two patients with locally inoperable tumours were referred for preoperative radiochemotherapy with 28–45 (mean 37) Gy and a combination of cisplatin (20 mg/m^2, days 1–5), 5-fluorouracil (400 mg/m^2, days 1–5) and folinic acid (100 mg/m^2, days 1–5). The chemotherapy cycle was repeated on day 29. A tumour response was recorded in 16 of the 22 patients and 14 of the 16 responding underwent secondary surgery. The 30-day mortality rate was 9 per cent, but the overall hospital mortality rate was 19 per cent for patients undergoing primary resection and 21 per cent for those treated by radiochemotherapy followed by secondary surgery. Reporting the 30-day mortality rate alone may conceal data and this should not be accepted as a measure of postoperative mortality. The incidence of surgical complications was comparable for the two groups (25 *versus* 21 per cent). Although general and, in particular, pulmonary complications were not specified, the authors concluded that preoperative radiochemotherapy for irresectable squamous cell carcinoma of the oesophagus does not increase postoperative mortality or morbidity rates.

Complications of anticoagulation therapy

A recent survey demonstrated that most hospitals in Germany rely on postoperative low-dose heparin treatment for the prophylaxis of deep vein thrombosis (DVT). Schmidt and associates[8] highlight two types of heparin-associated thrombocytopenia that may occur irrespective both of the type of heparin used and the route of administration, and which often go unrecognized. Type I has an incidence of 1–15 per cent and is a relatively harmless condition in which the platelet count falls temporarily. It is caused by inhibition of adenylate cyclase, resulting in decreased intracellular levels of adenosine 3',5'-cyclic monophosphate. Platelet counts are usually not lower than 10^{11}/l and will recover spontaneously even when heparin treatment is continued. This condition does not require specific treatment.

Type II heparin-associated thrombocytopenia has an estimated incidence of 0·6–10 per cent. An immunological mechanism is believed to cause platelet aggregation, resulting in a fall in platelet count to below 10^{11}/l. The condition may develop immediately following the first dose of heparin in already sensitized patients or 6–14 days after the first treatment in those not previously exposed to the anticoagulant. Up to 50 per cent of patients with type II thrombocytopenia develop arterial or venous thromboembolic complications. Thrombi consist mainly of fibrin–platelet aggregates, so-called 'white clots'. The condition is associated with a 25–30 per cent mortality rate from myocardial infarction, pulmonary embolism or mesenteric infarction, and the morbidity rate from arterial embolism, DVT, ischaemic infarction or paraparesis may be as high as 60 per cent. When heparin therapy is discontinued the platelet count returns to normal within 1 week. Treatment of overt thromboembolic complications consists of standard regimens including embolectomy and thrombolysis with streptokinase or urokinase. The authors recommend monitoring of platelet counts on alternate days to recognize the condition and list a number of sophisticated laboratory tests for verification. Anticoagulation may then be achieved by use of aspirin or dicoumarol.

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The American Journal of Surgery®

Dr Hiram C. Polk Jr, Editor of The American Journal of Surgery, *has this month selected from the July to September issues of that journal for his digest. A summary of the best of the* BJS, *written by Professor John Farndon, appears in the American journal.*

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Sepsis

There have been few subjects of broader interest over the past decade than the study of peritonitis and intra-abdominal abscess formation. Much has been learned about the process, although major clinical application of some of the new concepts has not yet been achieved. Simmen and Blaser[1] report interesting observations on 59 patients with infection; these indicate that infected peritoneal fluid is often acidic and relatively hypoxic compared with that from patients undergoing elective laparotomy. The diagnostic predictive value of this work may be far less important than its simple and direct contribution to the understanding of peritoneal infection. The significance of the relationship between these observations and *in vitro* susceptibility or antibiotic activity remains to be determined.

Upper gastrointestinal tract

The group of van der Mijle and associates[2] from Groningen in the Netherlands contributes further to the growing understanding of malfunction of the jejunal Roux limb, especially for reconstruction following gastric surgery. Earlier papers in *The American Journal of Surgery* indicated a motility disorder in the Roux limb itself that has little to do with the status of the residual gastric pouch. It is interesting to speculate whether an 'uncut' Roux limb would have the same characteristics.

Breast

Reconstruction of the female breast carried out following surgical treatment of breast cancer is very prevalent in North America and often employed as an index of quality of care. There has been concern that early complications and late tumour recurrence would be unfavourably influenced by this additional, often very extensive, procedure. O'Brien and associates[3] define these risks in a significant population of patients in a most reassuring way.

Cardiovascular

Some clinical reports have value, just for the simple fact that they remind the clinician of important and/or often overlooked relationships. Buchbinder and associates[4] describe the discovery of a variety of curious lesions in the evaluation of patients with relatively simple lower-extremity venous disease. The lesson of looking for the underlying disease process continues to be valid.

The surgical approach to brachiocephalic stenotic vascular lesions continues to be reported through a trickle of patients from some very busy centres. The principles that are evolving from a few large units are very important and directly influence safety, expense and extent of requisite care. Salam and associates[5] point out that extrathoracic bypass procedures for symptomatic proximal common carotid stenosis or occlusion were safe and well tolerated, with a 3-year patency rate in the range of 90 per cent and apparent protection against further carotid-related neurological deaths. With an ageing population, more and more of whom are seeking low-risk care, these kinds of observations are at least reassuring.

The number of operations performed in North America for cardiac disease has grown in a dramatic fashion over the past two decades and the indications for surgery have, more often than not, been extended. Lower-extremity arteries have been required as access for devices, especially the intra-aortic balloon pump, and a higher proportion of such patients develop leg ischaemia. This influences the outcome of the primary cardiac surgical procedure with significant morbidity and a mortality rate[6] that approaches 50 per cent. As indications for interventional less invasive surgical procedures are expanded, so the evaluation of the peripheral circulation is increasingly important to minimize such adverse outcomes.

Debate has continued over the management of carotid artery occlusion by endarterectomy. DeLaurentis and associates[7] studied this prospectively in 261 patients and found that a palpable stump pulse, pressure in the stump of the carotid artery and retrograde flow were accurately reflective of collateral blood flow, permitting them to carry out shunting in a selective fashion with excellent results.

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Growth factors and interleukins

Baigrie and colleagues[8] studied the utility of interleukins as markers in response to surgery of the abdominal aorta, notably excision and replacement. They postulated that portal endotoxaemia and related colonic ischaemia may be major contributors and related to interleukin (IL) 6 release. The majority of patients undergoing aortic surgery did not develop clinically significant colonic ischaemia but the study demonstrated a significant clinical correlation between frank ischaemia and altered IL-6 level, which may be helpful in the interpretation of the new physiological mediators.

The significance of growth factors in surgical illness and physiology is poorly understood. Their order of administration, dose and route of delivery are obviously critically important, but none of them appears at this time to represent anything like the pervasive influence of penicillin on Gram-positive coccal infection 50 years ago. The report by Ness and associates[9] addresses proliferative growth factors in breast cyst fluid and provides a degree of understanding in the illness of truly cystic breast disease. The therapeutic potential is discussed.

Colorectal cancer

Yamamoto and associates[10] examined some clinicopathological variants of mucinous carcinoma of the colon and rectum. This tumour is known to be associated with a poor prognosis, due largely to its tendency to invade directly into adjacent viscera and a propensity to more extensive lymph node involvement. The authors recommended extensive surgical excision when mucinous adenocarcinoma is discovered. Long-term results to test this hypothesis are awaited.

Trauma

For a very long time, the League of Nations' classification of cancer of the uterine cervix stood alone as a clinical scoring system with direct relevance to patient care. Recently there has been a proliferation of scores and grading systems for many surgical conditions, for example haemorrhoids and liver injury. This has been most clearly justified in the field of trauma, where standardization of protocols and evaluation of the impact of new treatment are critically dependent on the classification of the severity of injury. Increasing objectivity in grading that injury is vitally important. Rutledge and associates[11] from the University of North Carolina studied 428 consecutive victims of trauma and determined that intensive care unit and hospital outcomes were best predicted by the Acute Physiology and Chronic Health Evaluation II score. They caution that no combination of scoring methods is a substitute for clinical assessment and that scores are best employed alongside clinical judgements made by the clinician experienced in the field. This suggests that a number of the discrepancies seen in previous reports may be a reflection of the wisdom and experience of the attending surgeon.

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Factors influencing the hyperaemic response after carotid endarterectomy

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Transcranial Doppler ultrasonography was used to evaluate serially the changes in middle cerebral artery blood flow velocity (MCAV) in 37 consecutive patients during the first 72 h after carotid endarterectomy to identify factors that may predispose towards postoperative hyperaemia. Within 6 h of endarterectomy, median MCAV in the operated hemisphere was 48 per cent (95 per cent confidence interval 37–60 per cent) above that on admission and remained 27 per cent (95 per cent confidence interval 19–37 per cent) higher at 72 h. There was a similar, but less marked, increase in MCAV in the contralateral middle cerebral artery during the same time period. There was no association between the postoperative increase in MCAV and clinical presentation, admission MCAV, the presence or absence of a residual neurological deficit or infarction on computed tomography before operation, carotid clamp time, shunt usage, internal carotid artery stump pressure or MCAV during clamping. The greatest increase in MCAV was observed in patients with internal carotid artery stenosis $\geqslant 50$ per cent and, more particularly, in those with preoperative evidence of impaired cerebrovascular reserve. In the latter patients, MCAV was 100 per cent above the admission level within 12 h of operation and was still 50 per cent raised at 72 h.

Immediately after carotid clamp release and restoration of blood flow, there is usually a surge in middle cerebral artery blood flow velocity (MCAV) that then decreases within 10 min of clamp release, although not back to the preoperative level[1]. Evidence suggests that this initial phenomenon represents a short-lived hyperaemic response to the effects of carotid clamping and may reflect the ability of the collateral circulation to maintain cerebral blood flow (CBF) during carotid occlusion[1].

After this initial surge, some patients progress to a secondary hyperaemic phase that may persist for up to 5 days after surgery[2]. The true incidence of this secondary hyperaemic phase is unknown, but it is much commoner than the associated clinical symptoms. Fewer than 1 per cent of patients will suffer a stroke, usually due to intracerebral haemorrhage[3], but a greater proportion will have headache or disorientation[2,4]. It is generally thought that this phenomenon results from transient impairment or failure of cerebral autoregulation[2,3,5], secondary to a chronic state of cerebral vasodilatation in an attempt to maintain blood flow. The clinical manifestations tend to become apparent 24–72 h after operation, although evidence suggests that the initial increase in CBF develops well before this, and CBF may even be falling by the time of onset of symptoms[2].

This prospective study used transcranial Doppler (TCD) ultrasonography to evaluate serially changes in MCAV in 37 consecutive patients during the first 72 h after carotid endarterectomy with the aim of identifying factors associated with this phenomenon.

Patients and methods

Assessment before operation

Twenty-three of the 37 patients presented with a transient ischaemic attack (TIA) or amaurosis fugax. Fourteen presented with a completed stroke, 11 of whom had a persisting neurological deficit at the time of operation. No operation was carried out on stroke patients within 3 months of onset of symptoms. All patients underwent carotid angiography, computed tomography (CT), TCD ultrasonography and assessment of cerebrovascular reserve (CVR) before operation.

The degree of stenosis of the internal carotid artery was determined as the maximal biplane diameter reduction expressed as a percentage of the normal internal carotid artery diameter above the stenosis[6]. Thirty of the 37 patients had internal carotid artery stenosis $\geqslant 50$ per cent, eight of whom had stenosis between 50 and 70 per cent. Seven patients had internal carotid artery stenosis < 50 per cent and had been randomized to surgery in the European Carotid Surgery Trial before publication of the interim results. Ten patients had a localized region of hypodensity on CT consistent with an area of old infarction. Five recordings of MCAV were measured in both the symptomatic and asymptomatic hemispheres in the manner described by Aaslid and colleagues[7] together with measurements of blood pressure and end-tidal carbon dioxide. End-tidal carbon dioxide was measured, using an infra-red capnograph, from continuous samples of air drawn from a tight-fitting face mask. The measurement was made because of the known dependency of MCAV on arterial partial pressure of carbon dioxide ($P_{a\text{CO}_2}$)[8].

CVR was evaluated to assess the haemodynamic state of the cerebral circulation before operation. Above a critical internal carotid artery stenosis, the brain attempts to maintain normal CBF by progressive pial vasodilatation, which increases the cerebral blood volume (CBV). Thus, while CBF may be maintained at near-normal levels, the progressive increase in CBV means that the cerebral arterioles have a reduced capacity to undergo further vasodilatation when stressed (the concept of impaired CVR). Conventionally, CVR is evaluated by measuring the increase in either blood flow or blood flow velocity in response to a vasodilatory stimulus, such as inhaling carbon dioxide[6,9]. Using positron emission tomography[10], it has been shown that the most sensitive indicator of CVR is the ratio of CBF to CBV. This ratio is an alternative expression for the reciprocal of mean cerebral transit time (MCTT), and Gibbs *et al.*[10] proposed that measurement of MCTT could provide a simpler method of evaluating CVR.

The present study used a novel technique for imaging regional changes in MCTT to evaluate CVR. The theory, experimental confirmation and validation have been detailed elsewhere[11,12]. In summary, a bolus of $^{99\text{m}}$Tc-sodium pertechnetate was injected rapidly into an antecubital vein, with the patient lying supine in a head-extended position with the skull vertex over a small field of view γ camera, equipped with a high-sensitivity collimator. Sequential frames were acquired using a 32×32 matrix at a rate of $3\,\text{s}^{-1}$ for 1 min, by which time the examination was complete. The method generates a colour parametric image of regional MCTT, while the computer calculates the mean transit time for each hemisphere. The normal range of hemispheric

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MCTT (2·2–7·7 s) reflects the wide interindividual variability and the dependency of MCTT on end-tidal carbon dioxide[11]. Interhemispheric MCTT symmetry is, however, strictly maintained throughout the physiological range of end-tidal carbon dioxide[11,12] (median interhemispheric MCTT difference 0·2 (95 per cent confidence interval (c.i.) 0–0·6) s). In normal healthy volunteers an increase in end-tidal carbon dioxide causes a significant reduction in MCTT in both hemispheres (while maintaining interhemispheric MCTT symmetry) that correlates directly[12] with simultaneous increases in MCAV. Specifically, blood flow velocity changes[12] in direct proportion to the reciprocal of MCTT. Thus MCTT not only changes in the manner predicted through changes in MCAV, but also, because the reciprocal of MCTT is an alternative expression for CBF:CBV, the increase in MCAV (with increasing end-tidal carbon dioxide) measures changes in CBF:CBV, i.e. CVR.

In patients with haemodynamically significant extracranial internal carotid artery stenosis causing impaired CVR, the CBV increases to maintain CBF and there is a corresponding increase in MCTT. This, therefore, produces significant interhemispheric MCTT asymmetry, reflecting the change in CBF:CBV. Impaired CVR can thus be recognized by prolongation[11] of hemispheric MCTT beyond 7·7 s or by the development[11,12] of interhemispheric MCTT asymmetry $\geqslant 0{\cdot}7$ s. In this study, eight of the 37 patients had preoperative evidence of impaired CVR in the symptomatic hemisphere.

Surgical technique

Endarterectomy was performed under normotensive normocarbic general anaesthesia using systemic heparinization. All but one arteriotomy was closed with a vein patch and the nerve to the carotid sinus was not anaesthetized or divided in any patient. Systemic blood pressure and heart rate were measured continuously from a radial artery cannula and electrocardiogram respectively. A temporary indwelling shunt was employed in 19 patients using the criteria of slowing of the cerebral function monitor or internal carotid artery stump pressure < 50 mmHg. Systolic and mean ipsilateral MCAV were measured continuously throughout the operation[13].

Assessment after operation

On recovering from anaesthesia, two patients suffered a minor transient neurological deficit. One was thought to be embolic in origin and the other haemodynamic[13]. Both patients were confirmed to have a patent internal carotid artery using duplex ultrasonography. Serial measurements of MCAV, mean arterial blood pressure and end-tidal carbon dioxide were made every hour for the first 6 h and then again at 12, 24, 48 and 72 h in all patients. On each occasion, five measurements were taken from both the operated and non-operated middle cerebral artery, in addition to measurements of arterial blood pressure and end-tidal carbon dioxide. These values were then averaged and a mean calculated for each time period.

Statistical analysis

MCAV was not normally distributed (Filliben's test[14]) and so non-parametric analysis was used. Values in the text refer to the median (95 per cent c.i.). $P < 0{\cdot}05$ was taken as significant. Because of the normal range of interindividual variability[15] with regard to MCAV, data are presented as the percentage increase in systolic MCAV above the admission level, e.g. if the preoperative MCAV was 100 $\mathrm{cm\,s^{-1}}$ and rose to 120 $\mathrm{cm\,s^{-1}}$, this represents an increase of 20 per cent above baseline. This facilitates comparison between patients.

Results

Figure 1 illustrates a typical example of the two types of hyperaemic response after carotid endarterectomy. Note the initial surge in MCAV following release of the carotid clamps. This is followed by a transient decrease in MCAV, which then increases again to a peak of 210 $\mathrm{cm\,s^{-1}}$ 6 h after operation. In this example MCAV had returned to the preoperative level within 72 h. During this time, the patient suffered neither headache nor neurological morbidity.

Table 1 details the percentage increase in MCAV for the operated and non-operated hemispheres during the first 72 h after operation. *Table 2* shows the respective changes in mean arterial pressure and end-tidal carbon dioxide for each time period. Within 4–6 h of surgery, MCAV was 48 per cent (95 per cent c.i. 37–60 per cent) above the preoperative level in the operated hemisphere and 21 per cent (95 per cent c.i. 13–21 per cent) above baseline in the non-operated hemisphere. MCAV then gradually declined over the next 48 h but, at 72 h, remained 27 per cent (95 per cent c.i. 19–37 per cent) above the admission level in the operated hemisphere. This hyperaemic phase was not simply a consequence of concomitant changes in either mean arterial pressure or end-tidal carbon dioxide (*Table 2*) and could not be predicted from the preoperative MCAV value. Two patients recovered from anaesthesia with a transient minor neurological deficit. Both had an initial surge in MCAV on clamp release but neither developed a hyperaemic response over the ensuing 72 h.

Table 3 details the relationship between the percentage increase in MCAV and various parameters that might be associated with an increased likelihood of postoperative hyperaemia, if this were mediated by intraoperative ischaemic

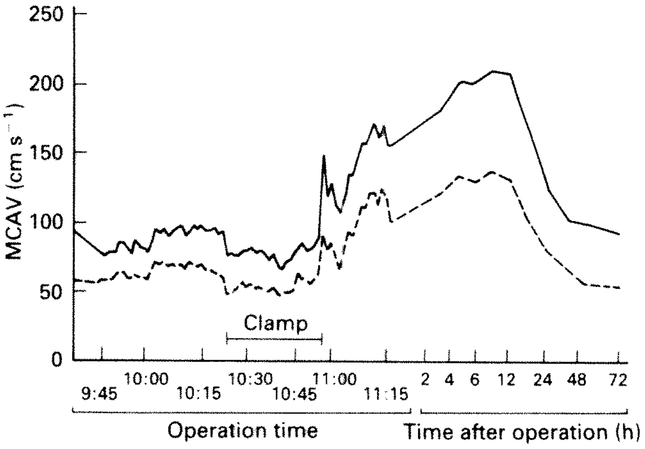

Figure 1 *Serial monitoring of systolic (——) and mean (– – –) middle cerebral artery blood flow velocity (MCAV) in the operated hemisphere during, and for 72 h after, carotid endarterectomy in a patient with preoperative evidence of impaired cerebrovascular reserve. Note the initial transient surge in MCAV immediately after carotid clamp release, followed by a more pronounced secondary hyperaemic phase over the next 24 h. At 12 h, MCAV was 100 per cent above the preoperative level*

Table 1 *Increase in middle cerebral artery blood flow velocity following carotid endarterectomy*

	Increase in MCAV (%)*		
Time after operation (h)	Operated side ($n = 37$)	Non-operated side ($n = 37$)	P†
1–3	42 (30–56)	17 (7–28)	<0·0001
4–6	48 (37–60)	21 (13–21)	<0·0001
12	45 (34–62)	22 (13–30)	0·001
24	38 (27–51)	13 (7–21)	0·002
48	26 (17–37)	10 (3–23)	0·018
72	27 (19–37)	14 (8–24)	0·003

* Values are median (95 per cent confidence interval). MCAV, middle cerebral artery blood flow velocity. † Wilcoxon signed rank test

Table 2 *Mean arterial pressure and end-tidal carbon dioxide following carotid endarterectomy*

Time after operation (h)	Mean arterial pressure (mmHg) ($n = 37$)	End-tidal carbon dioxide (mmHg) ($n = 37$)
Admission	100 (97–107)	38 (36–40)
1–3	83 (77–87)	42 (40–44)
4–6	83 (78–88)	41 (38–42)
12	84 (78–88)	39 (37–41)
24	93 (88–98)	39 (37–41)
48	96 (99–101)	38 (36–40)
72	102 (97–108)	39 (37–41)

Values are median (95 per cent confidence interval)

Table 3 *Increase in middle cerebral artery blood flow velocity above admission level during the first 72 h following carotid endarterectomy*

	Increase in MCAV (%)*			
	4–6 h	12 h	48 h	72 h
TIA or amaurosis fugax ($n = 23$)	51 (34–72)	45 (33–73)	28 (14–47)	29 (15–45)
Stroke ($n = 14$)	42 (28–58)	46 (27–72)	23 (9–40)	25 (13–40)
P†	0·94	0·93	0·67	0·92
Residual neurological deficit				
Present ($n = 11$)	32 (6–49)	39 (13–72)	17 (4–39)	22 (7–39)
Absent ($n = 26$)	55 (33–67)	47 (35–70)	28 (17–43)	29 (18–45)
P†	0·09	0·41	0·34	0·44
CT				
Infarct ($n = 10$)	41 (24–57)	54 (24–81)	38 (25–57)	34 (20–43)
Normal ($n = 27$)	51 (36–69)	41 (31–68)	20 (9–33)	24 (12–39)
P†	0·40	0·51	0·07	0·27
Carotid clamp time (min)				
< 25 ($n = 23$)	52 (39–68)	53 (37–77)	16 (2–33)	22 (5–39)
⩾ 25 ($n = 14$)	37 (22–69)	34 (23–66)	18 (7–32)	23 (10–44)
P†	0·24	0·11	0·16	0·40
Shunt usage				
Yes ($n = 19$)	56 (39–72)	59 (40–88)	35 (19–51)	33 (19–48)
No ($n = 18$)	39 (26–61)	34 (24–50)	18 (9–33)	21 (10–34)
P†	0·21	0·08	0·12	0·17
Internal carotid artery stenosis (%)				
⩾ 50 ($n = 30$)	55 (42–69)	50 (37–72)	29 (18–43)	28 (17–42)
< 50 ($n = 7$)	24 (9–34)	27 (7–49)	16 (2–33)	22 (5–39)
P†	0·01	0·04	0·21	0·68

*Values are median (95 per cent confidence interval). MCAV, middle cerebral artery blood flow velocity; TIA, transient ischaemic attack; CT, computed tomography. †Mann–Whitney *U* test

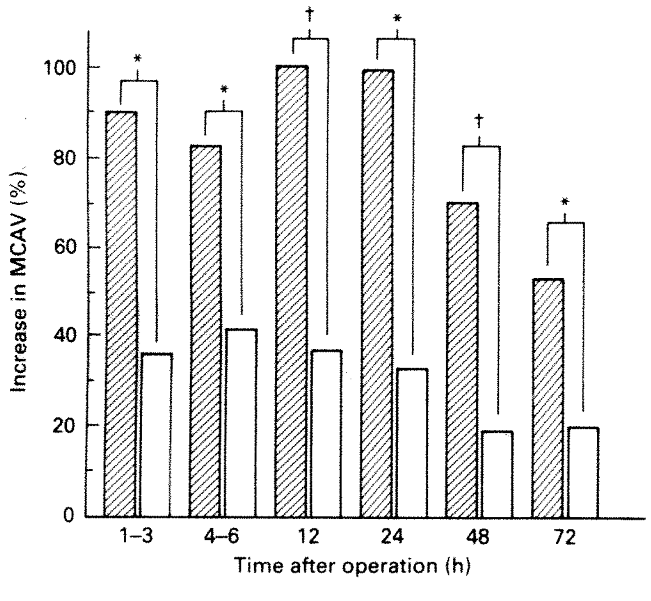

Figure 2 *Comparison of the median increase in middle cerebral artery blood flow velocity (MCAV) following carotid endarterectomy in patients with (▨) and without (☐) preoperative evidence of impaired cerebrovascular reserve.* *$P < 0{\cdot}05$, †$P < 0{\cdot}005$ *(Mann–Whitney U test)*

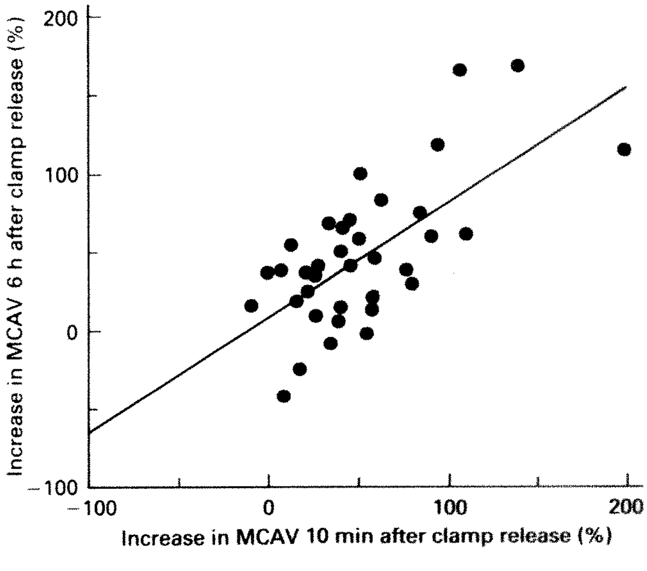

Figure 3 *Relationship between the increase in middle cerebral artery blood flow velocity (MCAV) (above the admission level) 6 h following surgery and the increase in MCAV measured 10 min after carotid clamp release and final restoration of flow.* $r_s = 0{\cdot}66$, $P < 0{\cdot}0001$

injury. There was no significant relationship between MCAV increase and mode of clinical presentation, or presence or absence of either a preoperative residual neurological deficit or CT infarct. Similarly, neither the duration of carotid clamping nor the use of a shunt appeared to influence the late hyperaemic response. There was, however, a significant trend for patients with extracranial internal carotid artery stenosis ⩾ 50 per cent to have a greater increase in MCAV than those with stenosis < 50 per cent. The strongest association was noted in patients with preoperative evidence of impaired CVR (*Figure 2*). Within 12 h of operation, MCAV had increased by 100 per cent (95 per cent c.i. 57–180 per cent) compared with only 37 per cent (95 per cent c.i. 27–47 per cent) ($P = 0.005$) in those with normal CVR. By 72 h, MCAV was still 53 per cent (95 per cent c.i. 39–106 per cent) above the admission level in patients with preoperative impairment of CVR as opposed to a 20 per cent (95 per cent c.i. 12–30 per cent) increase in MCAV in those with normal CVR ($P < 0.05$). None of these patients suffered any neurological morbidity although two described minor ipsilateral headache.

As can be seen in *Figure 1*, the secondary hyperaemic phase began almost immediately after the initial surge in MCAV following carotid clamp release; this was typical of the other patients in this series. There was no association between the secondary hyperaemic response and the initial surge in MCAV that immediately followed restoration of flow. There was, however, a clear association between the magnitude of MCAV increase at 6 h and the increase in MCAV 10 min after clamp release (*Figure 3*), suggesting that the secondary response was already gaining momentum at an early stage.

Discussion

The advent of TCD ultrasonography has enabled investigators to study non-invasively many of the physiological effects of carotid endarterectomy on cerebral haemodynamics. Principal advantages of the technique include the ability readily to perform intraoperative and postoperative bedside examinations with the minimum of inconvenience to the patient. One should, however, be aware that a measurement of MCAV cannot be directly converted into absolute volume flow, as velocity varies in proportion to the second power of the vessel radius, while volume flow changes in accordance with the fourth power. However, provided that P_{aCO_2} (which is one of the most powerful mediators of cerebrovascular tone) remains constant, it has become conventional[8] to assume that changes in MCAV provide an index of change in CBF.

This study has shown that, within 6 h of operation, MCAV was 48 per cent higher than before surgery in the operated hemisphere and was also 21 per cent higher in the non-operated hemisphere. This phenomenon was not mediated by concomitant changes in either mean arterial pressure or end-tidal carbon dioxide. These results are similar to those reported by Schroeder *et al.*[16] using the intravenous xenon technique, who noted a 37 per cent increase in CBF in the operated hemisphere within 24 h of surgery and a 33 per cent rise in the non-operated hemisphere. Quite why the hyperaemic response should be bilateral remains unclear.

As in the present study, Schroeder *et al.*[16] found no association between the magnitude of the postoperative hyperaemic reponse and preoperative clinical presentation, CT findings, internal carotid artery stump pressure or the use of an indwelling shunt, which suggests that the increase is probably not a reflection of intraoperative ischaemia. Although these authors did not evaluate CVR, they did measure an index of cerebral perfusion pressure by calculating the ratio of mean internal carotid artery to common carotid artery pressure. In patients with a ratio < 0.7, the increase[16] in CBF at 24 h was 60 per cent as opposed to only 24 per cent in those with a ratio > 0.7; this was the only factor predictive of significant hyperaemia in their series. A low internal carotid artery to common carotid artery pressure ratio reflects the fact that the perfusion pressure distal to severe internal carotid stenosis is reduced as a consequence of inadequate collateral circulation. In this situation, CBF is maintained by progressive cerebral arteriolar vasodilatation[10]. This situation is analogous to that in the patients in the present study with impaired CVR, who also exhibited the greatest increases in MCAV following operation. Like Schroeder *et al.*[16], the present authors observed that the hyperaemic phase was more prolonged in these patients and MCAV remained 50 per cent above the admission level at 72 h. These findings suggest a temporary impairment of cerebral autoregulation. Patients with preoperative impairment of CVR enter surgery with varying degrees of pial vasodilatation, and some may be approaching a state where the resistance vessels are maximally dilated[17]. After surgery there is a surge in blood flow through the dilated arteries which are unable to recover their normal vasomotor capacity for some days[17]. Clearly, the majority do not suffer any ill effects, but evidence suggests that those with coexistent episodes of hypertension may be more vulnerable to neurological morbidity[2], and blood pressure should be carefully controlled during this phase[15].

This study also suggests that the hyperaemic response starts almost immediately after carotid clamp release and final restoration of flow. The authors have previously shown that immediately after clamp release there is usually a transient surge in MCAV that appears to be a response to the effects of carotid occlusion and reflects the capacity of the collateral circulation to maintain flow during clamping[1]. No association was found between this primary hyperaemic response and the secondary phenomenon but, as *Figures 1* and *3* illustrate, there is a clear trend for the increase in MCAV to recur after the initial surge and then continue for many hours thereafter. Moreover, we agree with Schroeder *et al.*[16] that the later hyperaemic response is unlikely to result from intraoperative hypoperfusion injury during clamping, as there was no association between the subsequent MCAV increase and the level of MCAV during clamping, shunt usage or carotid clamp time.

In summary, this study has shown that there is a bilateral hemispheric hyperaemic response following carotid endarterectomy, especially in the operated side. The greatest and most prolonged increase in MCAV was observed in patients with preoperative evidence of impaired CVR. These findings support the observations of others that the phenomenon is probably due to transient postoperative impairment of vasomotor tone and cerebral autoregulation, which then normalizes over the first few days after operation.

Acknowledgements

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Case report

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Spontaneous staphylococcal peritonitis in an otherwise healthy young man

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Spontaneous peritonitis caused by *Staphylococcus* species is rare, and has previously been reported only in immunocompromised patients or in association with continuous ambulatory peritoneal dialysis. An otherwise healthy patient with this condition is described.

Case report

A 28-year-old Caucasian man, who had previously been well, presented with a 12-h history of colicky abdominal pain and nausea. Some 2 weeks previously he had been treated empirically with antibiotics for a chest infection. On examination he had pyrexia (37·5°C) with generalized peritonitis. Abdominal radiography was normal. The haemoglobin level was 14·8 g/dl with a white cell count of $18 \cdot 8 \times 10^9$/l (83 per cent neutrophils). A diagnosis of appendicitis was made.

At laparotomy the peritoneal cavity was seen to have been totally replaced by thin adhesions and the small bowel was slightly distended with prominent vasculature and lymphatics. There were no localizing features of appendicitis or duodenal perforation. Biopsies of the adhesions were taken for histological and bacteriological assessment, and the abdomen was closed.

Histological examination showed fibrofatty tissue with fibrin and acute inflammation. *Staphylococcus aureus* was grown from the swab and biopsies of the adhesions taken during surgery, and the patient was treated with flucloxacillin and gentamicin. After operation he had prolonged ileus requiring 3 weeks of parenteral nutrition. At 5 weeks the man was tolerating a normal diet and was discharged home. He remains well at 6 months.

Discussion

Spontaneous ('primary') bacterial peritonitis is an infection of the peritoneum that occurs without perforation of an abdominal organ or penetration of the abdominal wall. It is most often associated with ascites, in which case the most common bacteria are Gram-negative bowel organisms. It is extremely rare in normal healthy adults[1].

The proposed routes of infection in spontaneous bacterial peritonitis are haematogenous, via internal female genital organs and by transmural migration. Animal experiments[2,3] have shown that inoculation of the blood or internal female genital organs with bacteria does not consistently produce bacterial peritonitis. Transmural migration has been suggested as the most likely pathogenesis in ascitic peritonitis. This condition is usually associated with an oedematous bowel wall in which, it is proposed, the usual barriers to bacteria are not effective.

The clinical picture in the present patient with fibrous adhesions may be due to the *Staphylococcus* being coagulase-positive and therefore tending to form adhesions. The only similar cases previously reported are sclerosing peritonitis as a reaction to practolol[4], which was not implicated in the present case, and the abdominal cocoon[5], which has previously been reported only in young women living in tropical or subtropical areas and is described as a dense fibrous capsule around the small bowel.

Similar patients have not been described in the literature and the prognosis is uncertain, but the man remains well at 6 months.

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Randomized controlled trial of patch angioplasty for carotid endarterectomy

*A randomized controlled trial was performed to evaluate patch angioplasty for patients undergoing carotid endarterectomy. There were 213 patient episodes affecting 148 men and 65 women, with 109 allocated to patch angioplasty. Following surgery six patients suffered transient ischaemic attacks but these did not delay discharge from hospital. Six individuals (four patched operations, two not patched) required re-exploration for postoperative haemorrhage and eight (two patched procedures, six not) had potentially serious neurological problems after operation. Of these eight patients, four (none receiving patch angioplasty) underwent re-exploration and in each case a clot was removed and a patch inserted; three of the four made a good long-term recovery. The other four patients suffered completed strokes from which one died. Two further patients (one patched procedure, one not) died after operation from myocardial events, giving an overall 30-day stroke or mortality rate of 2·8 per cent. Objective follow-up assessment with duplex scanning at 1 year was completed by 94·8 per cent of patients; significantly more vessel restenoses and occlusions were observed in those not receiving patches (*P < 0·01*). Patch angioplasty reduces the number of immediate postoperative complications, and significantly lowers vessel restenosis and occlusion rates at 1 year after operation.*

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Recent reports have confirmed the benefits of carotid endarterectomy for patients with high-grade carotid stenosis who have had associated cerebrovascular events[1,2]. Government policy[3] in the UK now includes commitment to a 40 per cent reduction in the number of strokes within the next 10 years.

The value of patch angioplasty after carotid endarterectomy has not yet been determined. Many feel that inclusion of a patch lengthens the clamp or shunt time, makes the procedure technically more demanding[4,5], may be unnecessary in some patients[6], and may put patients at risk of infection or aneurysm formation[7]. Others believe that use of a patch may reduce the number of both perioperative and later neurological complications and may prevent vessel stenosis at arterial closure and subsequently[8].

Many reports have been published on the subject of patching but several are essentially retrospective reviews of experience before and after introduction of the method[4,5,9]. Others, although prospective in design, are observational studies that failed to randomize patients[8,10–13]. Three prospective randomized studies have been reported[6,14,15] but in each of these a substantial proportion of cases (19 of 159, 30 of 152 and 46 of 164 respectively) was not randomized. Despite these problems all three suggested a benefit in favour of patch angioplasty over simple closure in terms of reduced restenosis rate; some also showed a reduction in the incidence of perioperative neurological events.

This paper reports results of a prospective randomized trial undertaken to examine the value of patch angioplasty for patients undergoing carotid endarterectomy; the surgical method was in strict accordance with randomization.

Patients and methods

A total of 199 patients undergoing 213 consecutive carotid endarterectomies at four participating centres (Belfast, Leicester, Portsmouth, Southampton) were recruited prospectively. Each was randomly assigned, using sealed envelopes, to receive either simple vessel closure or patch angioplasty. The age and sex distribution of the study cohort reflected the prevalence of carotid vessel disease in the general population, with similar groups being entered from each centre (*Table 1*).

Of 213 operations, 196 (92·0 per cent) were for symptomatic disease, 124 (58·2 per cent) for transient ischaemic attack, 42 (19·7 per cent) for amaurosis fugax and 30 (14·1 per cent) were carried out after a good functional recovery from stroke. The remaining 8·0 per cent of operations were for high-risk situations with high-grade asymptomatic stenosis affecting one carotid artery and with occlusion of the contralateral vessel. Whenever possible patients were treated with aspirin before surgery.

All patients were assessed before carotid endarterectomy by duplex scanning, the results of which could be supplemented with arteriography if necessary. An observed frequency shift of 3·8 kHz using a 4-MHz transducer was taken to indicate intermediate-grade stenosis of ≥50 per cent reduction in luminal cross-sectional diameter. A lesion creating high-grade stenosis of ≥75 per cent of the cross-sectional diameter had the same observed frequency shift using the same transducer, plus a positive compression test observed at the ipsilateral supraorbital artery. Eight symptomatic patients were operated on for low-grade (<50 per cent) stenosis. Some 84 operations were for intermediate-grade stenosis and the remainder for high-grade stenosis (*Table 1*).

At operation a shunt was used when technically possible, with full heparinization in all cases. The choice of patch material was made by the individual surgeon; two centres used autologous vein ($n = 53$) and two Dacron (Du Pont, Stevenage, UK) ($n = 56$). The duration of clamping was not recorded. At 3 and 12 months after operation each patient was re-examined with a duplex scanner for evidence of vessel restenosis or occlusion, using the same criteria for stenosis as were applied before endarterectomy.

Results

Patch angioplasty was used in 109 operations and simple non-patch arteriotomy closure in 104; there was no deviation from randomization. In the immediate postoperative period six patients (four undergoing patching, two not; *P* not significant) suffered haemorrhage or haematoma formation requiring a return to theatre.

After six operations (2·8 per cent; three patched, three not)

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Table 1 *Patient age, sex and degree of preoperative vessel stenosis as determined by duplex scanning*

Centre no.	No. of patients	Sex ratio (M:F)	Mean age (years)	No. of carotid endarterectomies	Preoperative vessel stenosis*		
					<50%	50–74%	75–99%
1	93	2·5	68·3	98	7	39	54
2	56	1·5	63·2	64	1	28	71
3	38	2·0	64·3	38	0	53	47
4	12	3·0	66·0	13	0	54	46
Total	199	2·2	65·9	213	3·8	39·4	56·8

*Values are percentages

Table 2 *Outcome for vessels examined at 3 months and 1 year after carotid endarterectomy with and without patch angioplasty*

	Patched	Not patched	*P**
Operated	109	104	
Occluded by 30 days	0	6	<0·05
Follow-up at 3 months			
Vessels available for follow-up	107	98	
Examined	94 (87·9)	84 (86)	n.s.
Cumulative occluded vessels	1	7	<0·05
Vessel stenosis ⩾50%	9	9	n.s.
Follow-up at 1 year			
Vessels available for follow-up	104	92	
Examined	99 (95·2)	87 (95)	n.s.
Cumulative occluded vessels	2	9	<0·05
Vessel stenosis ⩾50%	4	8	n.s.
Total occlusion or stenosis at 1 year	6	17	<0·01

Values in parentheses are percentages. *χ^2 test; n.s., not significant

Table 3 *Deaths and complications after carotid endarterectomy with and without patch angioplasty*

	Patched	Not patched
Haemorrhage with return to theatre	4	2
Death within 30 days		
Non-stroke	1	1
Stroke	0	1
Death at 1–12 months		
Non-stroke	4	9
Stroke	0	1
Total deaths	5 (4·5)	12 (12·5)
Neurological event within 30 days		
TIA	3	3
Prolonged recovery	0	3*
Stroke	2	2
30-day stroke or mortality rate	3 (2·8)	3 (2·9)
Neurological event at 1–12 months		
TIA	1	2
Prolonged	0	1†

Values in parentheses are percentages. TIA, transient ischaemic attack. *One patient died; †patient died

patients suffered a transient neurological event with no late sequelae. After eight other operations (3·8 per cent; two patched, six not) patients suffered serious neurological events, with effects lasting more than 24 h. After four of these operations (all unpatched) patients developed symptoms within 24 h of surgery. Each of these individuals underwent immediate re-exploration with thrombectomy and vessel closure using a patch; three made a full functional recovery with time. Each of these four episodes is counted as vessel occlusion within the original group in the subsequent analysis. However, where vessel patency was re-established by exploration and patching, each episode is counted in the patched group when considering outcome for restenosis at the 3-month and 1-year time points.

The remaining serious neurological events were completed strokes that developed later in the postoperative course; these were not treated by re-exploration. Two of these strokes (after patch operations) occurred despite there being a patent operated vessel on duplex examination, while cerebral infarction occurred in a patient receiving non-patched closure with an occluded operated vessel as revealed by post-mortem examination. Within 30 days of surgery two further patients died from myocardial infarction (one from each group).

At hospital discharge or by 30 days (whichever was the shorter), a total of six operated vessels had occluded, all without patches. During the subsequent year 14 further patients died (four patched operations, ten not; *P* not significant). Of these only one patient, who had undergone a non-patch operation, suffered a stroke and the operated vessel was shown to be occluded. Three patients suffered further symptoms, one patient receiving patch angioplasty in whom the vessel had occluded and two without patches.

At 3-month follow-up 94 of 107 (87·9 per cent) patched and 84 of 98 (86 per cent) non-patched vessels were re-examined (*Table 2*). Nine stenoses and one additional occlusion were detected in each group. At one year, five of the nine significant stenoses found in patients with patched closure at 3 months had regressed and no new lesion had developed. Only two stenoses regressed in the non-patched group and one new lesion developed (*Table 2*). Between 3 months and 1 year one further patched and two non-patched vessels asymptomatically occluded.

The results summarized in *Table 2* reveal that at all stages of follow-up significantly fewer vessels were occluded after patch angioplasty. Deaths and complications, other than neurological morbidity, did not vary significantly in incidence between the two groups, although more events occurred after simple closure (*Table 3*). No significant infections or aneurysms developed in either group. Analysis of the vein-patched and Dacron-patched subgroups did not show any difference with respect to the incidence of postoperative complication, neurological event, vessel occlusion or vessel restenosis.

Discussion

The present fully randomized study confirms the conclusions drawn by others[4–6,8–13,15]. First, there is an absence of early vessel occlusion after patch angioplasty. Second, there is a significant reduction in vessel occlusion and restenosis rates at 3 months and 1 year after surgery. Third, there is a trend towards lower mortality and morbidity rates after patch angioplasty.

Significant carotid artery restenosis of over 50 per cent occlusion may affect between 10 and 20 per cent of patients within 2–5 years of surgery[10,16,17]. Although vessel occlusion may occur at any stage, it most commonly develops in the immediate period after surgery; this occurs in about 2 per cent of cases[10,15], and morbidity and mortality rates become considerable if it is left untreated. In the longer term, between

1 and 2 per cent of all patients will have recurrence of symptoms from carotid restenosis[18,19].

Most restenoses develop in the early months after endarterectomy; Aldoori and Baird[20] have suggested that all recurrent lesions are detected within 6 months of operation. In the present study, therefore, with 95 per cent of patients being re-examined within 1 year, the vast majority of significant stenoses that are likely to develop will have been detected. The regression of stenosis detected by duplex scanning in the early months after endarterectomy is also well recognized[20]. This occurred in seven patients in the present study.

The benefits of patch angioplasty must be considered alongside its disadvantages. The use of a patch increases clamping time[4,5] by between 15 and 30 min. Suture-line disruption, leading to haemorrhage or false aneurysm formation, has been reported after both conventional and patched vessel closure. However, the incidence of these problems appears to be greater after patching, particularly if autologous vein is used and especially if this is harvested from the ankle saphenous or external jugular vein. Infection seems to be a much rarer cause for these complications[7]. In the present study no patient developed an infective or aneurysmal complication in the 1-year follow-up period. Six patients were returned to the operating theatre for haemorrhagic complications, four after patching and two after simple closure, but patch angioplasty did not seem to be associated with an excess of directly related complications.

Many reports have advocated a selective approach to the use of patch angioplasty for patients considered particularly at risk of restenosis or vessel occlusion, i.e. those with small vessels or those undergoing surgery for restenosis. The present results, however, do not allow identification of these subgroups specifically. It is concluded that patching is of benefit in the short and medium term; it may well be beneficial in reducing the long-term recurrent stenosis rate.

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Popliteal aneurysm: morphology and management

Since January 1988, 32 patients have presented with 44 popliteal aneurysms (22 thrombosed, 22 non-thrombosed). Patients with thrombosed aneurysms were older (median age 72 versus *66 years), and more likely to have bilateral lesions* ($P < 0.02$) *and serious associated cardiovascular disease* ($P < 0.02$). *Nineteen aneurysms thrombosed acutely; 12 were treated with intra-arterial thrombolysis, which was at least partially successful in seven. All 12 were subsequently bypassed, as were the other seven which were associated with such severe ischaemia that they required urgent operation. One patient died and two others required major amputation. Other complications included foot-drop (two patients), renal failure (one) and wound infection (two). Two grafts thrombosed and required re-exploration. Elective bypass was carried out in 11 patients without acutely thrombosed aneurysms; there were no significant postoperative problems. Distortion within the aneurysm* ($P < 0.01$), *large size* ($P < 0.01$) *and distortion of the popliteal artery above or below the lesion* ($P < 0.02$) *were all associated with thrombosis. Stenosis within the aneurysm was more likely in patients with multiple lesions* ($P < 0.01$) *and distortion with larger aneurysms* ($P < 0.01$). *After correcting for distortion, none of the other variables was independently significant. The combination of distortion and diameter >3 cm was present in 13 of 15 thrombosed aneurysms. Morbidity is high following acute thrombosis of popliteal aneurysm. Distortion of the aneurysm appears to be a more sensitive predictor of thrombosis than size alone. The combination of distortion with a diameter >3 cm may help to define popliteal aneurysms that should be bypassed electively.*

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There are two main controversies in the management of popliteal aneurysm. These concern the management of asymptomatic aneurysms and the treatment, once the run-off has been cleared, of aneurysms that have thrombosed. There are few data on the natural history of popliteal aneurysm. A recent review suggested an average annual thrombosis rate of 14 per cent in asymptomatic aneurysms, but with a wide range of 5–24 per cent per year[1]. This is almost certainly because popliteal aneurysms are a heterogeneous group of lesions; some are small and uncomplicated whereas others are larger, distorted, multiple or associated with stricture.

Early reports[2,3] highlighted the high amputation rate associated with acute thrombosis of popliteal aneurysm. It has therefore become accepted treatment to operate on the lesion once it has been diagnosed to prevent thrombosis occurring[4–6]. This view has recently been challenged for the following reasons. First, an asymptomatic patient is subjected to potential morbidity and mortality[7]. Second, with newer forms of treatment, particularly intra-arterial thrombolysis (IAT), the results of treating thrombosed aneurysms might be better than have previously been reported[8]. Finally, with the widespread use of duplex ultrasonography, minor degrees of popliteal dilatation are being identified; their relationship with clinical aneurysm is uncertain.

The aim of this paper is to review the authors' experience of popliteal aneurysm in an attempt to define those that are at risk of thrombosis. The management and outcome of thrombosed aneurysm is described.

Patients and methods

Data were collected prospectively as part of a continuing audit. All patients with asymptomatic aneurysms underwent arteriography and ultrasonography. For thrombosed aneurysms, IAT was regarded as the treatment of choice in the presence of a viable limb. The technique and results of IAT have been described previously[9–11]. The lytic agent was infused through a 5–7-Fr catheter placed in the ipsilateral femoral artery; streptokinase (5000 units/h) or tissue plasminogen activator (0·5 mg/h) were used. Even if thrombolysis was not successful in clearing the run-off, the aneurysm was often cleared sufficiently to allow a comparison of the radiological appearance of thrombosed and non-thrombosed lesions.

Popliteal aneurysm was defined[5] as a localized dilatation of the popliteal artery >2 cm in diameter or >150 per cent of the normal proximal arterial calibre[12].

Statistical analysis was carried out using the χ^2 test with Yates' correction, the Mann–Whitney *U* test or Student's *t* test as appropriate.

Results

During 5 years from January 1988, 32 patients presented with 44 popliteal aneurysms. Twenty patients presented with a thrombosed popliteal aneurysm; in two of these a contralateral aneurysm thrombosed within 6 weeks of initial presentation. Thus, there were 22 thrombosed aneurysms in this series, of which 19 thrombosed acutely. Eleven other patients had non-thrombosed aneurysms (one bilateral). Presenting features of non-thrombosed aneurysms included distal emboli in two and local discomfort in one. The remainder were asymptomatic. All of these aneurysms were atherosclerotic. One further patient presented with a mycotic aneurysm. He was excluded from the analysis. There was only one woman in the series.

Patients

The clinical details of patients with thrombosed and non-thrombosed popliteal aneurysms are shown in *Table 1*.

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Patients with thrombosis were older and more likely to have serious associated cardiovascular disease than those with non-thrombosed lesions ($P < 0{\cdot}02$). Furthermore, there was a greater chance of an aneurysm being present on the contralateral side in patients presenting with thrombosis ($P < 0{\cdot}02$).

Aneurysms

Thrombosis of the aneurysm was significantly associated with distortion (*Figure 1*; *Table 2*), either within the aneurysm ($P < 0{\cdot}01$), or above or below it ($P < 0{\cdot}02$). There was no significant correlation between stenosis and thrombosis, although multiple aneurysms were more likely to have stenoses along their length ($P = 0{\cdot}009$). Thrombosed aneurysms were significantly larger than those that had not thrombosed; nevertheless, one of the thrombosed lesions was only 1·2 cm in diameter. Bilateral aneurysms were significantly bigger than unilateral lesions ($P = 0{\cdot}002$). The combination of distortion within the aneurysm and size >3 cm was associated with thrombosis in 13 of 15 cases. On the other hand, when neither of these features was present, only two of 19 aneurysms had thrombosed.

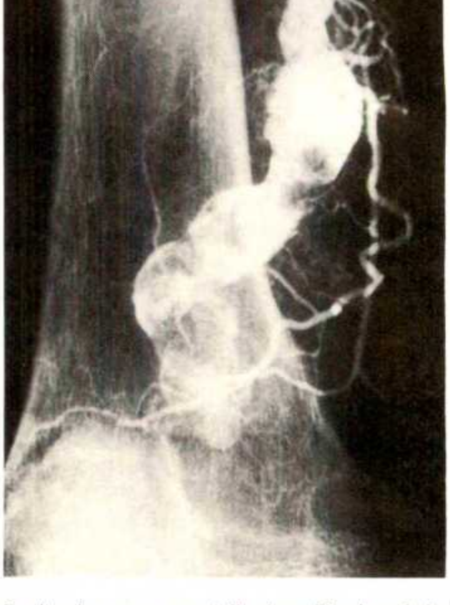

Figure 1 *Popliteal aneurysm partially cleared by thrombolysis, showing gross distortion within the lesion*

Management

The management of the 22 thrombosed aneurysms is shown in *Figure 2*. Of the three patients with chronic thrombosis, all were claudicants, but two were not incapacitated and so were treated conservatively. The remaining patient underwent ligation and bypass of the aneurysm. Of the 19 patients presenting with acute thrombosis, 12 were initially treated with IAT. This proved completely successful in clearing the run-off in six patients and partially so in one other. A further patient underwent partially successful thrombolysis for symptoms due to distal emboli from an aneurysm. In five patients the thrombolysis failed. In each, the procedure had to be terminated owing to complications: bleeding in three and significant worsening of the clinical condition of the limb in two. Seven patients underwent immediate operation as their legs showed signs of neurological impairment on admission. A total of 20 patients therefore underwent ligation and bypass of the aneurysm. Six fasciotomies were performed. Two limbs required amputation following attempts at revascularization. In retrospect, both of these were probably non-viable at the time of presentation, having presented after considerable delay. The complications sustained by these patients are shown in *Table 3*.

Eleven patients with non-thrombosed aneurysms were operated on. All three symptomatic patients had bypass of the aneurysm. All of the asymptomatic lesions operated on were large aneurysms associated with distortion. There were no postoperative complications. None of the aneurysms treated conservatively subsequently thrombosed (median follow-up 18 months).

Table 1 *Patient details*

	Thrombosed aneurysm	Non-thrombosed aneurysm	*P*
No. of patients	20	11	—
Median (range) age (years)	72 (53–83)	66 (52–76)	n.s.*
Other aneurysm present			
Abdominal aortic	8	4	n.s.†
Popliteal	11	1	<0·02†
Femoral	1	1	n.s.†
No. of patients with associated cardiovascular disease	14	2	<0·02†
Myocardial infarction	3	1	
Angina	2		
Congestive heart failure	2		
Arrhythmia	2		
Cerebrovascular accident	6	1	
Hypertension	4		

*Mann–Whitney *U* test; †χ^2 test with Yates' correction; n.s., not significant

Table 2 *Morphology of popliteal aneurysms*

	Thrombosed aneurysm	Non-thrombosed aneurysm	*P*
Distortion within aneurysm	10 of 15*	0 of 21	<0·01†
Distortion above or below aneurysm	10 of 14*	4 of 21	<0·02†
Stenosis within aneurysm	7 of 15*	3 of 21	n.s.†
Stenosis above or below aneurysm	6 of 14*	3 of 21	n.s.†
Sacular	1	1	n.s.†
Fusiform	18	20	
Single	10	17	n.s.†
Multiple	9	4	
Median (range) diameter (cm)	3 (1·2–4·2)	2 (1·0–3·7)	0·007‡

*Totals do not correspond with total in series: if the aneurysm was not cleared of thrombus its morphology could not be defined. †χ^2 test with Yates' correction; ‡Mann–Whitney *U* test; n.s., not significant

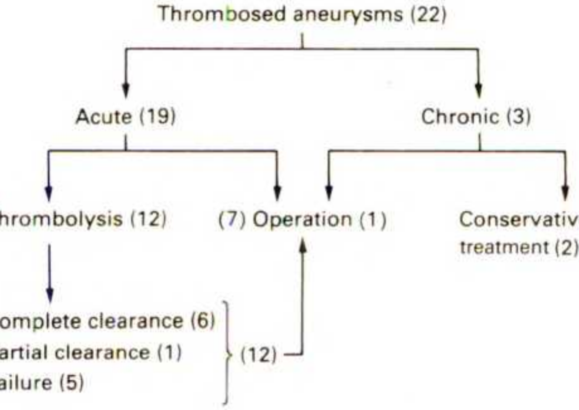

Figure 2 *Management of 22 thrombosed popliteal aneurysms*

Table 3 *Complications of treating thrombosed popliteal aneurysms**

	Thrombosed aneurysm
No. of operations	20
Death	1
Amputation	2
Re-exploration	2
Foot-drop	2
Wound breakdown	2
Renal failure	1
Intra-arterial thrombolysis	
Bleeding	3
Acute limb deterioration	2

*No complications occurred after 11 operations on non-thrombosed aneurysms

Discussion

Over a 5-year period 32 patients presented with 44 popliteal aneurysms, a higher rate than is apparent in most other series. It may be that the prevalence of popliteal aneurysm is increasing but it is more likely that the condition is being diagnosed more efficiently. In other reports patients with chronic occlusion may have been treated for peripheral vascular disease without the recognition of an underlying aneurysm. Popliteal aneurysm may also have been underdiagnosed as a cause of acute ischaemia before the use of thrombolysis. The ratio of thrombosed to non-thrombosed aneurysms in the present series was 1:1, similar to that described by others[13]. The ratio of popliteal to abdominal aortic aneurysm (AAA) has been described[5] as approximately 1:15. During the 5-year period of the present study, about 300 patients with AAA presented, yielding a ratio of 1:8.

The association of popliteal aneurysm with other aneurysms, particularly AAA, is well documented and was confirmed in the present series. Patients with thrombosed lesions were more likely to have an aneurysm on the other side, and bilateral lesions were bigger than single ones. That patients with thrombosed aneurysms were older and had more serious cardiovascular disease may suggest that thrombosis represents a more advanced stage in the disease process. The rate of thrombosis varies from one series to another, but the present results suggest that some aneurysms are at greater risk of thrombosis than others. Although the aim of IAT is to clear run-off, it also allows detailed analysis of the morphology of the aneurysm. Distortion of the aneurysm and its size were the most important risk factors, and a combination of distortion and diameter >3 cm was present in 87 per cent of aneurysms that had thrombosed. Distortion probably represents the extent to which elongation and dilatation of the artery have occurred. The resulting tortuosity may be related to thrombosis due to kinking or turbulence.

Amputation rates of up to 30 per cent have been reported following thrombosis, with an average in the literature of 18 per cent[1]. The mortality rate is also high in these patients. Rates of mortality and limb loss are much reduced in asymptomatic patients. Long-term graft patency and limb salvage rates are also better in patients operated on before thrombosis of the aneurysm[1]. Nevertheless, serious complications may occur when operating on asymptomatic patients, such that some are made worse by a prophylactic operation. Clearly, identification of aneurysms at high risk of thrombosis would be useful in minimizing the number of patients undergoing elective operation.

If the limb is viable on presentation, IAT should be considered as the treatment of first choice in clearing the run-off. However, the technique itself is not without complications; reported rates of stroke and major bleeding are 1 and 5 per cent respectively[14]. Minor bleeding and catheter-related problems occur in up to 25 per cent of cases[10]. A further complication recently reported[15] is that of acute deterioration of the limb during IAT. This appears to be more common in thrombolysis of popliteal aneurysms and occluded grafts than in that of thrombosed atheromatous arteries. This complication occurred in two patients in the present series, at a time when thrombolysis appeared to be progressing satisfactorily. In both cases an urgent thrombectomy and bypass was carried out, with satisfactory results. This phenomenon is probably due to massive thrombus destabilization followed by distal embolization. Passing the perfusing catheter through the aneurysm to direct lysis at the run-off alone may be a better way of dealing with thrombosed aneurysms than attempting to lyse the aneurysm thrombus itself.

The present results suggest that there are significant morphological differences between thrombosed and non-thrombosed aneurysms. The presence of the abnormalities described in this paper might persuade the surgeon to consider elective operation in an otherwise asymptomatic aneurysm.

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Physical examination and selective conservative management in patients with penetrating injuries of the neck

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This prospective study of 335 patients with penetrating injuries of the neck examined the decision whether to operate or observe according to a protocol based mainly on physical examination. Emergency angiography was performed in only three patients. Sixty-six patients (20 per cent) were subjected to emergency operation because of signs and symptoms suggestive of significant injury (60 patients) or because of positive investigations (six). The remaining 269 patients (80 per cent) were selected for non-operative management. Two of these patients (0·7 per cent) required elective operation during the initial hospital stay. No deaths occurred in patients treated conservatively. Some 192 (72 per cent) of observed patients were available for early follow-up and 111 (42 per cent) for late follow-up. No significant complications were found. Physical examination is a reliable method for detecting significant injuries following penetrating neck trauma. Emergency angiography is rarely necessary.

Some trauma centres practise routine exploration of all neck injuries that penetrate the platysma, but most advocate some form of selective conservative management. Methods of patient selection vary widely. Many[1–3] believe that physical examination alone is unreliable and that significant injuries may be missed. An alternative to routine exploration is the liberal use of angiography and other investigations[1,2,4]. Others[5–7] believe that physical examination is reliable in detecting significant injuries. Most of the existing studies are retrospective and few include late follow-up of patients managed conservatively. A large prospective study was therefore undertaken to include late follow-up of observed patients to assess the reliability of physical examination.

Patients and methods

Patients with injuries violating the platysma and involving the anterior neck were recruited between 1989 and 1991. Those who died before admission to the trauma unit were excluded. The location of the injury was classified by zones: zone I included the base of the neck from the clavicles to the cricoid cartilage; zone II included the area between the cricoid cartilage and the inferior border of the mandible; and zone III comprised the area from the inferior border of the mandible to the base of the skull.

Patients with one or more of the following signs underwent emergency surgery: severe active bleeding, shock not responding to intravenous resuscitation, large expanding haematoma, absent or diminished peripheral pulse, air bubbling through the wound and major haemoptysis. Chest radiography was performed whenever there was suspicion of an associated chest injury and provided that the patient was stable.

In the absence of the above signs the patient was assessed whenever possible by careful digital exploration of the wound. This was to assess the direction of the injury track, i.e. towards or away from vital structures. No attempt was made to palpate adjacent major vessels, in case this precipitated bleeding. Some patients with subcutaneous emphysema were assessed by Gastrografin (Schering, Johannesburg, South Africa) swallow and endoscopy. If digital exploration or the entrance and exit sites of a bullet suggested that the direction of the wound track was away from the larynx, trachea and oesophagus, no further investigations were performed. Patients with painful swallowing or hoarseness were investigated by Gastrografin swallow or endoscopy. Doppler pressure measurements were obtained whenever it was difficult to palpate the pulses. Emergency angiography was performed only in haemodynamically stable patients with a widened mediastinum on erect chest radiography. Semielective angiography was performed whenever a bruit or abnormal peripheral pulse was detected after admission to the trauma unit. Patients with isolated brachial plexus injuries were operated on electively, within 24–72 h of injury.

Patients selected for non-operative management were admitted for observation for 24–48 h. They were discharged with instructions to return to the hospital if they experienced pain, discomfort or bleeding. Early and late outpatient assessment was carried out.

Results

Patients

The study group comprised 304 men and 31 women of mean age 28 (range 16–62) years. Of these, 283 (84 per cent) sustained a knife wound, 39 (12 per cent) a gunshot wound and 13 (4 per cent) injury by other sharp instruments. The left side of the neck was involved in 74 per cent of instances. Zone I was involved in 44 per cent of patients, zone II in 29 per cent and zone III in 27 per cent. Clinical findings on admission are shown in *Table 1*.

Investigations

Chest radiography was performed in 250 patients. The most common findings were: emphysema in the neck (56 patients),

Table 1 *Clinical presentation on admission and type of treatment for 335 patients*

Symptom or sign	No. of patients	Conservative treatment	Surgical treatment
Active bleeding	68	40 (59)	28 (41)
Blood pressure <90 mmHg	61	41 (67)	20 (33)
Haematoma	100	81 (81)	19 (19)
Abnormal peripheral pulse	5	0 (0)	5 (100)
Bruit	3	1 (33)	2 (67)
Dyspnoea	12	8 (67)	4 (33)
Subcutaneous emphysema	55	34 (62)	21 (38)
Haemoptysis	6	2 (33)	4 (67)
Dysphagia	3	0 (0)	3 (100)
Haematemesis	1	0 (0)	1 (100)
None of the above	116	113 (97)	3 (3)

Values in parentheses are percentages

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Table 2 *Management according to the site of wound*

Site of wound	No. of patients	No. of patients undergoing surgery	No. of patients with significant injuries
Zone I	148	22 (15)	15 (10)
Zone II	95	28 (29)	26 (27)
Zone III	92	18 (20)	17 (18)
Total	335	68 (20)	58 (17)

Values in parentheses are percentages

Table 3 *Injured structures in 58 therapeutic operations*

Vascular	
Internal jugular vein	15
Subclavian vessels	9
External jugular vein	6
Carotid artery	4
Vertebral artery	4
Innominate vessels	2
Small named vessels	10
Total	50
Visceral	
Trachea	13
Pharynx	4
Larynx	3
Oesophagus	4
Thyroid gland	7
Total	31

haemopneumothorax (47) and a widened mediastinum (two). A Gastrografin swallow was performed in 18 patients with subcutaneous emphysema and a wound track towards the midline; this demonstrated oesophageal leakage in two patients. Endoscopic evaluation of the oesophagus and trachea was performed in five patients with subcutaneous emphysema or minor haemoptysis; tracheal injuries were found in two. Doppler pressures did not reveal any new information that was not detected clinically. Emergency angiography was performed in only three patients: in two because of a widened mediastinum on chest radiography and in one for a knife blade embedded at the base of the skull. One angiogram demonstrated a fistula between the aorta and the subclavian vein, and one a fistula between the innominate vessels. Both patients with an abnormal angiogram had a murmur on auscultation. Four later angiograms were carried out because of bruits detected after admission to the trauma unit. There was one fistula between the subclavian artery and the internal jugular vein, one intimal tear of the subclavian artery and two negative studies.

Management

Sixty-six patients (20 per cent) underwent emergency surgery on the basis of clinical signs (60 patients) or positive investigations (six). In ten of these operations no significant injuries were found. The remaining 269 patients (80 per cent) were selected for conservative management. Two of these patients required semielective surgery for vascular lesions, during the same hospitalization. In both a bruit was detected the day after admission and angiography demonstrated an arteriovenous fistula.

Table 2 demonstrates management according to the site of injury. The injured organs in the 58 patients with significant trauma are listed in *Table 3*. Of the nine patients with brachial plexus injury, only one was subjected to emergency operation because of an associated vascular lesion. The remaining eight patients were operated on electively for nerve repair.

Six (15 per cent) of patients with low-velocity bullet injuries required an operation compared with 57 (20 per cent) of those with knife wounds.

Morbidity and mortality rates and length of hospital stay

There were two deaths from massive bleeding in patients treated surgically. There were no deaths in the group of 269 patients initially selected for non-operative treatment. Of the conservatively treated group, 192 (72 per cent) returned for early follow-up within 1 month (mean 16 days) of discharge. Five patients had wound sepsis but neither aneurysm nor fistula. Of the rest, 111 (42 per cent) had a late follow-up, more than 1 month (mean 48 days) after discharge; no complications were found. Seventy-five patients (28 per cent) in the observed group were lost to follow-up; most of these patients had given false addresses. The mean hospital stay of patients treated conservatively was 2·6 days, that of patients subjected to non-therapeutic operation 3·5 days and that of those who underwent therapeutic surgery 7·7 days.

Discussion

The management of penetrating injuries of the neck remains controversial. Many[1–3] believe that physical examination is unreliable. Sclafani *et al.*[1] found that physical examination had a specificity of 80 per cent and a sensitivity of 61 per cent. Meyer *et al.*[8] in a prospective study found clinical examination to have an accuracy of only 68 per cent. Some[3,9,10], therefore, recommend exploration of all wounds that have violated the platysma. The incidence of unnecessary or negative explorations is high if this policy is followed, ranging from 46 to 89 per cent[2,8,11].

Triage criteria may vary considerably from clinical examination and observation alone to various invasive diagnostic tests. Many[2,4,11] recommend routine arteriography for all injuries in zones I and III, but only a few patients benefit. Meyer *et al.*[8] reported only nine positive angiograms in a series of 113 patients with zone II injuries who underwent routine angiography. Jurkovich *et al.*[2] found that only 9·4 per cent benefited from angiography. In the present series only 5 per cent of patients with zone I injuries and 13 per cent of those with zone III injuries had significant vascular lesions.

The reported incidence of false-positive and false-negative angiograms is 3 per cent each[2,8,12]. These figures are similar to the accuracy of physical examination in the present series. As angiography was not performed routinely, some arterial injuries may have been missed. This is, however, unlikely, because early and late follow-up of a significant number of observed patients did not show any vascular sequelae. Virtually all post-traumatic vascular lesions manifest within 3 months and the majority[13–15] within 1 month. Clinically occult angiographically detected vascular injuries have a good prognosis without surgery[12,16,17]. Many authors suggest that angiography in patients with zone I and III injuries may help in planning the incision, should operation become necessary. Depending on the operative findings, however, the exposure can be improved by adding a sternotomy or by anterior subluxation of the jaw. There is often poor correlation between angiographic reports and operative findings, and careful clinical examinations are reliable in detecting significant injuries. The accuracy of 97 per cent compares favourably with that of angiographic investigation. The reported low accuracy of physical examination may result from various factors: retrospective studies may not provide full details and trauma centres that practise mandatory exploration or rely on routine angiography may place too little emphasis on physical examination.

There is no argument that the presence of 'hard' signs is diagnostic of significant injury and emergency operation is needed. 'Soft' signs such as shock responding to resuscitation, minor active bleeding, haematoma, dyspnoea, subcutaneous emphysema, hoarseness, dysphagia or minor haematemesis are not an absolute indication for operation. These patients should be assessed individually, taking account of the direction of the injury track and the severity and type of 'soft' signs. Subcutaneous emphysema is considered by some[2,7] an indication for surgery but only 38 per cent of such patients in the present study needed an operation.

If the direction of the wound track is towards midline structures, contrast swallow studies and/or endoscopy are performed. Missed oesophageal or tracheal injuries may lead to adverse effects especially in the thoracic oesophagus but the cervical oesophagus may be more resilient. Ngakane *et al.*[18] showed that small oesophageal and tracheal injuries can be safely managed without operation. Some 80 per cent of patients with penetrating injuries of the neck can be safely managed conservatively. The decision whether to operate or observe can be made on the basis of careful initial and repeated clinical examinations. With this policy, only ten patients underwent unnecessary operation, only seven had an unnecessary arteriogram and there was no mortality or serious morbidity.

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Timing of extubation after oesophagectomy

Ventilatory support for 24 h after surgery is standard practice in many units after oesophagectomy, especially for patients in whom respiratory problems are anticipated. Weaning difficulties may occur, however, and there is increasing evidence that mechanical ventilation is associated with alveolar trauma. A deliberate change in policy was instituted in the authors' unit in January 1990 to make early extubation mandatory in all patients undergoing elective oesophagectomy, apart from those in whom serious perioperative problems were encountered. The present study compared two sets of patients: group 1 ($\mathrm{n} = 36$*) underwent oesophagectomy in the year before the policy change and group 2 (*$\mathrm{n} = 45$*) oesophagectomy in the year after. The two groups were similar in age, sex and respiratory risk factors. Early extubation was carried out in 38 patients in group 2 compared with eight in group 1 (*$\mathrm{P} < 0{\cdot}001$*). Only two patients in group 2 required prolonged ventilation compared with ten in group 1 (*$\mathrm{P} < 0{\cdot}005$*). No patient in group 2 required reventilation compared with seven in group 1 (*$\mathrm{P} < 0{\cdot}005$*), and no patient in group 2 who had undergone early extubation required delayed ventilation. The mean ventilation time and length of stay in the intensive care unit were significantly reduced following the policy change. Early extubation after elective oesophagectomy is an attainable goal and results in a significant reduction in both the morbidity rate and cost of surgery.*

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Respiratory complications are the main cause of morbidity after oesophagectomy[1–3]. Anaesthetic policy on ventilatory support after surgery varies considerably between units; it has become standard practice in many to ventilate patients overnight after operation on the assumption that this may minimize the number of respiratory complications[4,5]. Many of these patients experience weaning difficulties[6], and failed extubation is associated with high morbidity and mortality rates[7]. Pulmonary oedema has been attributed to alveolar barotrauma resulting from artificial ventilation[8]. Others[9,10] have attributed alveolar injury to overdistension with subsequent oedema.

An audit of oesophageal resection in the authors' unit revealed that respiratory complications may have been related to increasing use of overnight ventilation after oesophagectomy. A decision was made that all subsequent patients would be extubated in theatre immediately after oesophagectomy or shortly after admission to the intensive care unit. Patients were monitored closely to identify respiratory compromise or the need for repeated ventilatory support. This study examined the effect of this change in policy on morbidity and mortality rates, and intensive care and hospital stay in patients undergoing elective oesophagectomy.

Patients and methods

All patients undergoing oesophagectomy in the authors' unit have undergone a standardized preoperative investigation since 1987 and all details of their history, investigations, surgery, pathology and postoperative course have been collected prospectively and entered into a 128-field database (Reflex; Borland/Analytica, Scotts Valley, California, USA). Patients undergoing elective oesophagectomy during the period 1 January 1989 to 31 December 1989 were arbitrarily designated group 1.

A policy of early extubation after elective oesophagectomy was introduced in this unit in January 1990. After operation all patients, apart from the most seriously compromised, were required to be extubated in the theatre or on return to the intensive care unit. Patients undergoing elective oesophagectomy during the period 1 January 1990 to 31 December 1990 comprised group 2.

Patients who were not extubated by midnight on the day of operation but who underwent extubation the following day were defined as requiring overnight ventilation. Those who could not be extubated on the first day after surgery were considered as requiring prolonged ventilation. Patients who were extubated but required subsequent ventilatory support were classified as needing reventilation. Those who were not ventilated overnight but who subsequently required ventilation were deemed to have received delayed ventilation.

Statistical analysis

χ^2 analysis with Yates' correction, Fisher's exact test, the Wilcoxon rank sum test and Student's t test were used as appropriate.

Results

Forty-seven patients underwent oesophagectomy in 1989. Eleven undergoing pharyngolaryngo-oesophagectomy were excluded, leaving 36 for analysis in group 1. In 1990, 53 patients underwent oesophagectomy. Of these, three received emergency resection and five required pharyngolaryngo-oesophagectomy,

Table 1 *Preoperative assessment*

	Group 1 ($n = 36$)	Group 2 ($n = 45$)
Mean age (years)	66·1	66·8
Sex ratio (M:F)	2·3:1	1·4:1
COAD (%)	16	14
Smokers (%)	52	66
History of cardiac disease (%)	16	13
Mean FEV_1 (litres)	2·08	2·27
Mean FEV_1/FVC (%)	71	68
Median ASA grade	II	II
Mean P_{aO_2} (kPa)	11·72	10·72
Mean albumin level (g/l)	37·0	34·6

COAD, chronic obstructive airway disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; ASA, American Society of Anesthesiologists; P_{aO_2}, arterial oxygen tension

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Table 2 *Type of oesophagectomy*

	Group 1 (n = 36)	Group 2 (n = 45)
Three-stage	17	21
Two-stage (abdomen and chest)	6	22
Transhiatal	13	2

$\chi^2 = 14\cdot3$, 2 d.f., $P < 0\cdot001$ for all operation types; $\chi^2 = 11\cdot3$, 1 d.f., $P < 0\cdot001$ for those with and without thoracotomy

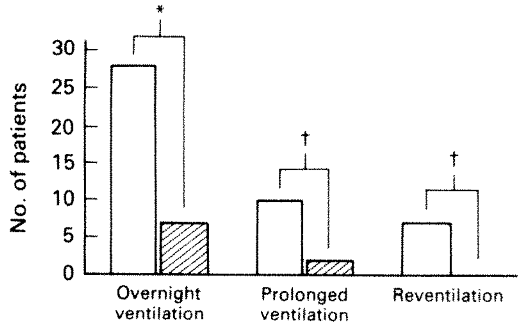

Figure 1 *Number of patients ventilated overnight or requiring prolonged ventilation or reventilation.* □, *Group 1* (n = *36*)*;* ▨, *group 2* (n = *45*). *P < *0·001*, †P < *0·005* (*Fisher's exact test*)

Table 3 *Postoperative complications*

	Group 1 (n = 36)	Group 2 (n = 45)	P*
Pleural effusion	23 (64)	28 (62)	n.s.
Atelectasis or consolidation	30 (83)	33 (73)	n.s.
Cardiac complications	16 (44)	5 (11)	<0·005
Sepsis	7 (19)	3 (7)	n.s.
Metabolic derangement	4 (11)	2 (4)	n.s.

Values in parentheses are percentages. *χ^2 test; n.s., not significant

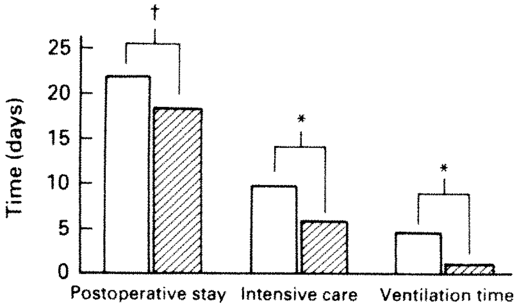

Figure 2 *Mean postoperative stay, intensive care stay and time on ventilator.* □, *Group 1;* ▨, *group 2.* *P < *0·05*, †P *not significant* (*Wilcoxon rank sum test*)

leaving 45 for analysis in group 2. The two groups were similar in age, sex and respiratory risk factors (*Table 1*). There was a difference in the type of operation performed (*Table 2*) in that more patients required thoracotomy in 1990 ($P < 0\cdot001$). Epidural analgesia was used routinely in the postoperative period in both years of the study.

After elective oesophagectomy, 28 of the 36 patients in group 1 received ventilation overnight compared with seven of the 45 in group 2 ($P < 0\cdot001$). The mean difference between the preoperative arterial oxygen tension and the first reading after extubation was similar in the two groups (0·35 *versus* −1·08 kPa, $P = 0\cdot18$). Two of the 45 patients in group 2 required prolonged ventilation compared with ten of the 36 in group 1 ($P < 0\cdot005$). No patient in group 2 required reventilation compared with seven in group 1 ($P < 0\cdot005$) (*Figure 1*). None of the 38 patients in group 2 who had undergone early extubation required delayed ventilation.

There was no increase in respiratory morbidity rate associated with the change in policy. In fact, cardiac complications were significantly fewer in group 2 (*Table 3*). The mean(s.e.m.) ventilation time was reduced from 4·6(1·3) to 1·1(0·7) days ($P < 0\cdot05$) and the mean(s.e.m.) length of intensive care fell from 9·8(1·6) to 5·9(0·8) days ($P < 0\cdot05$). The mean(s.e.m.) total postoperative stay was reduced from 22·1(2·6) to 18·5(2·0) days (P not significant) (*Figure 2*). The 90-day hospital mortality rate was also reduced from 17 per cent (six patients) in group 1 to 4 per cent (two) in group 2 ($P = 0\cdot07$).

Discussion

There is increasing evidence that mechanical ventilation is potentially harmful. Ventilator-induced pulmonary oedema is well recognized and produces pulmonary changes similar to those of adult respiratory distress syndrome[8,10–12]. Patients who are most likely to receive postoperative ventilation, i.e. those with poor respiratory reserve, may be at most risk of developing ventilator-related complications[13]. Some authors[8,13–15] have attributed these changes to trauma from high-pressure ventilatory support; others[9,11] have shown that similar changes may be produced by overexpansion. Dreyfuss and Saumon[16] recently advocated that the term volutrauma should be used in preference to barotrauma. The two mechanisms may have a synergistic role[17]. Thus, Hernandez *et al.*[10] showed that, in an animal model, chest wall restriction limited lung injury induced by high airway pressure.

Initial attempts at weaning may be unsuccessful in as many as 25 per cent of patients receiving short-term ventilation[18,19]. Those on prolonged ventilation are more likely to require many days for weaning and may take as long as a few months[20]. Respiratory muscle strength and maximum voluntary ventilation are reduced in undernourished patients[21]. Depletion of oxidative enzymes in the respiratory muscles, which are crucial to endurance in breathing, occurs within the first 3 days of complete mechanical ventilation[22]; the more prolonged the assistance the less likelihood of successful weaning. Demling *et al.*[7] found that failed extubation in surgical patients on the intensive care unit was associated with a morbidity rate of 50 per cent and a hospital mortality rate of 40 per cent.

Much work has centred on the investigation of parameters for successful weaning of patients receiving ventilation. Preoperative indices have not proved reliable predictors of weaning difficulty. Pulmonary function before surgery, age, sex and history of smoking were not associated with postoperative extubation outcome in patients undergoing cardiac surgery[23]. Many authors have looked at postoperative indices such as vital capacity, minute ventilation, maximal inspiratory pressure and maximum voluntary ventilation. The predictive power of such indices for successful weaning, however, has been poor[19,24,25]. Immediate postoperative extubation can be performed safely in most patients undergoing thoracotomy[26]. Quasha *et al.*[27] showed that early extubation after coronary artery bypass grafting was associated with a reduced cardiopulmonary morbidity rate. In the present authors' unit, a policy of early extubation was successfully introduced and was accompanied by a reduction in the number of cardiac complications. It appears that many of the problems of mechanical ventilation and weaning can be obviated by avoiding postoperative ventilation.

Patients who receive prolonged mechanical ventilation pose enormous clinical and ethical problems. Severe psychological stress is induced in such patients, their relatives and the intensive care nursing staff. In addition, these patients represent a heavy financial burden on hospital administrations[28]. In a recent audit of work in the authors' unit, it was calculated that the cost to the hospital of 1 patient-day in intensive care was IR£550 compared with IR£130 in a ward bed[29]. Using these figures, the observed reduction in the time in intensive care produced a mean saving per patient of IR£1638 for elective oesophagectomy in 1990.

Although there was no difference between the two groups in age, sex, tumour type and stage, or preoperative risk factors such as smoking, pulmonary function or cardiac history, there was a difference in the type of operation performed: more patients in group 2 had a thoracotomy. Transhiatal oesophagectomy has been advocated as the procedure of choice in high-risk patients because it was initially felt to be associated with fewer respiratory complications[30]. Shahian *et al.*[31] found higher morbidity rates associated with extrathoracic oesophagectomy than transthoracic resection. It is now felt that both operations have a place but that they result in similar morbidity and mortality rates[32–34]. The larger number of patients receiving a transthoracic approach in group 2 is unlikely to have influenced the outcome and, if anything, would probably have biased the results against these patients. The reduction in the number of transhiatal oesophagectomies in group 2 does not reflect a difference in patient selection (*Table 1*) but results from concern over one specific complication (chylothorax), which we have shown to be more frequent after transhiatal oesophagectomy[35] and which occurred in two of 13 patients in group 1. When the subgroup who underwent transhiatal oesophagectomy was excluded from the analysis, it was found that the difference between the two groups persisted.

In conclusion, early extubation after elective oesophagectomy does not result in increased respiratory morbidity rates. It is associated with a significant reduction in the number of cardiac complications, ventilation time and length of intensive care, and this has significant cost-saving implications. In the absence of reliable predictive indices of successful weaning, early extubation should be the goal in all patients. With adequate non-narcotic pain control, intensive preoperative patient counselling and perioperative physiotherapy, this can be successfully and safely achieved in the majority of cases.

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Short myotomy for vigorous achalasia

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Vigorous achalasia has been considered an indication for surgery, in which a thoracic approach is recommended for extending the myotomy along the whole of the oesophageal body to the point where manometry shows high-amplitude waves. Clinical results and postoperative manometric findings in 16 patients with vigorous achalasia undergoing abdominal surgery with myotomy limited to the lower oesophageal sphincter (LOS) were analysed to assess whether extended myotomy is necessary in surgery for this form of achalasia. The clinical results were excellent or good in all cases. Surgery induced a significant decrease ($P < 0.01$) in the diameter of the oesophagus as determined radiologically. The most significant postoperative manometric changes were a decrease in the resting pressure of the LOS and oesophageal body, a lowering of wave amplitude at all levels of the oesophagus, and a reduction in the proportion of repetitive waves. The results suggest that vigorous achalasia can be treated surgically in the same way as classical achalasia and question, at least from a therapeutic viewpoint, the use of the term vigorous achalasia.

The term vigorous achalasia was first coined by Olsen *et al.*[1] in 1957 to describe a variant of idiopathic achalasia characterized by the appearance of both simultaneous and high-amplitude contractions of the oesophageal body. Later, some investigators[2–6] defined vigorous achalasia by the additional criterion of repetitive contractions. However, the manometric criteria for defining the condition have been arbitrary[4,5,7]. Patients with vigorous achalasia have been reported to have less oesophageal dilatation and more chest pain than those with the classical type[2,5–7]. Nevertheless, there has been no direct comparison of manometric, radiographic and clinical findings in classical and vigorous achalasia, in spite of the introduction of modern manometric techniques. Some authors[8,9] consider that the distinction between these two types of achalasia has little clinical importance and that it might usefully be abandoned.

From a therapeutic viewpoint, vigorous achalasia has been thought to have a poorer response to dilatation than the classical variety[2,3]. For this reason, it has been considered an indication for surgical treatment in which a thoracic approach allows Heller's myotomy to be extended along the whole of the oesophageal body to the point where manometry shows pressure waves of above-normal amplitude[10–12]. However, some studies[13,14] have reported good results with dilatation, similar to those obtained in classical achalasia.

The aim of this study was to analyse the clinical results and postoperative manometric findings in 16 patients with vigorous achalasia who underwent abdominal surgery with myotomy of the lower oesophageal sphincter (LOS) not extended to the oesophageal body, to assess whether the term vigorous achalasia is useful in indicating myotomy involving a thoracotomy or whether there is no difference between treatment for this and the classical form.

Patients and methods

Patients

Of a total of 1298 patients admitted to the Digestive Motility Unit between January 1980 and January 1991, 102 showed clinical, radiological, endoscopic and manometric evidence of idiopathic achalasia. Of the 102 patients, 25 were considered to have vigorous achalasia because the mean amplitude of contractile waves was above normal (values considered normal in the authors' laboratory are shown in *Table 1*) and/or pressure waves were normal but more than 50 per cent were repetitive (three or more pressure peaks). Patients who had an associated longitudinal myotomy of the oesophagus via a thoracotomy (five patients) and those who refused to undergo postoperative manometry (four) were excluded. Of the 16 subjects studied, 11 were men; the median age was 50 (range 20–65) years. The mean duration of symptoms was 1·7 years (range 3 months to 10 years). Symptoms were, in order of frequency, dysphagia and substernal pain (100 per cent), regurgitation (81 per cent) and weight loss (25 per cent). Radiological examination showed a pointed distal oesophagus in all cases and a median oesophageal diameter of 4 (range 2·5–5) cm. All patients underwent endoscopy to exclude organic pathology. Dilatation was not attempted in any patient.

Surgical technique

The abdominal oesophagus and cardia were isolated via a supra-umbilical median laparotomy. Traction was applied to the oesophagus with a ribbon, and an 8–10-cm myotomy performed on the anterior distal oesophagus, extending for 1 cm on to the gastric wall. The gastric fundus was then mobilized behind the abdominal oesophagus, creating a posterior partial fundoplication of approximately 270° with suture of the stomach to each of the edges of the myotomy[15].

Postoperative evaluation

All patients underwent clinical, radiological, endoscopic, manometric and pHmetric evaluation. Clinical assessment was carried out annually by personal interview, and the results were considered excellent, good, fair or bad, as described by Vantrappen and Hellemans[13]. The median follow-up was 4 (range 1–14) years. A gastro-oesophageal barium

Table 1 *Manometric results in normal subjects in the authors' laboratory*

Lower oesophageal sphincter	
Total length (cm)	3·5 (2–4)
Intra-abdominal length (cm)	2 (1·1–2·5)
Mean resting pressure (mmHg)	13·5 (10·6–24·2)
Percentage relaxation	92 (83–100)
Oesophageal body	
Amplitude of contractile waves (mmHg)	65·6 (40·3–118·0)
Mean duration of contractile waves (s)	4·2 (2·8–5·6)
Percentage of tertiary waves	0 (0–0)
Percentage of repetitive waves	0 (0–0)

Values are median (range)

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study and manometric evaluation were performed 1–2 years after operation. The results were compared with preoperative values. Endoscopy was also performed every 2 years after surgery, and 24-h pH monitoring between 1 and 6 years after operation.

Manometry

Oesophageal manometry was performed using a probe with three microtransducers (Gaeltec, Dunvegan, UK) located at the distal end 120° radially to one another and spaced 5 cm apart and a 7754B System polygraph (Hewlett–Packard, Palo Alto, California, USA)[15]. Mid-respiratory LOS pressure relative to the gastric baseline was measured by the slow pull-through technique. Total length was calculated as the length of the sphincter between the initial rise above the gastric baseline and the return of the tracing to the oesophageal baseline. Intra-abdominal length was calculated as the length of the sphincter between the initial rise above the gastric baseline and the respiratory inversion point. The LOS pressure, as well as the value of its total and intra-abdominal length, represents a mean of values from the three transducers. The oesophageal body was divided into thirds and in each the following parameters were studied: mean amplitude of contractile waves, mean duration of contractile waves, mean percentage of tertiary waves and mean percentage of repetitive waves (three peaks or more). Mean basal pressure in the lower third of the oesophageal body was also calculated.

pHmetry

Continuous 24-h intra-oesophageal pH monitoring was performed using a PHM62 Standard Digital Precision pHmeter (Radiometer, Copenhagen, Denmark), a GK2801C combined glass-reference pH electrode (Radiometer) and a Hewlett–Packard polygraph, which has a continuous-current amplifier (Medium Gain DC Pre-Amplifier 8802A) for recording pH on heat-sensitive paper. The method has been described elsewhere[15]. Following the criteria of Johnson and DeMeester[16], reflux was considered pathological when the proportion of total time at pH < 4 was more than 4·5 per cent.

Table 2 *Manometric results in the lower oesophageal sphincter before and after surgery for vigorous achalasia in 16 patients*

	Before operation	After operation	*P**
Mean resting pressure (mmHg)	20·1 (12·0–52·5)	10·5 (6·7–31·4)	<0·05
Total length (cm)	3·5 (2–4)	3·7 (2–4·5)	n.s.
Intra-abdominal length (cm)	2·2 (1·0–3·5)	3·0 (1·8–4·5)	n.s.
Percentage relaxation	44 (0–61)	10 (0–70)	n.s.

Values are median (range). *Wilcoxon rank sum test for paired data; n.s., not significant

Statistical analysis

The Wilcoxon rank sum test for paired data was used for statistical comparison.

Results

Clinical

Clinical results were excellent in 12 patients and good in four. Classification of the four patients as 'good' was due to the presence of occasional mild thoracic pain, associated with occasional dysphagia in one. Only one patient showed symptoms of gastro-oesophageal reflux, which were alleviated with attention to diet and posture, and the use of antacids.

Radiology

Postoperative radiology showed that the narrowing of the oesophagogastric junction had disappeared in all patients, and that the median oesophageal diameter had been reduced from 4 (range 2·5–5) to 2·5 (range 2–3·5) cm (*P* < 0·01).

Endoscopy

Endoscopy findings were normal in all but one patient, in whom grade I oesophagitis was observed according to the Savary–Miller classification.

pHmetry

Continuous 24-h pH monitoring disclosed pathological gastro-oesophageal acid reflux in only one patient (the proportion of time at pH < 4 was 17·6 per cent).

Manometry

As shown in *Table 2*, surgery did not involve any significant changes at the LOS, except in mean resting pressure, which dropped significantly. *Table 3* shows a significant decrease in mean resting pressure in the oesophageal body after surgery. There was a significant postoperative decrease in the mean amplitude of waves and in the mean percentage of repetitive waves at all levels of the oesophagus. In addition, postoperative peristaltic waves appeared in the upper and middle thirds (*Table 3*).

Discussion

Olsen *et al.*[1] introduced the term vigorous achalasia in 1957 to designate a variant of idiopathic oesophageal achalasia that, from a manometric viewpoint, presented the characteristics of achalasia and idiopathic diffuse oesophageal spasm. In the absence of oesophageal peristalsis (achalasia) there were

Table 3 *Manometric results in the oesophageal body before and after surgery for vigorous achalasia in 16 patients*

	Before operation	After operation	*P**
Mean resting pressure (mmHg)	−1·2 (−7 to 6)	−9 (−13·5 to −1·5)	<0·01
Lower third of oesophageal body			
Mean amplitude of contractile waves (mmHg)	67·8 (33·4–130·0)	21·1 (2·4–63·8)	<0·01
Mean duration of contractile waves (s)	3·5 (2·0–5·2)	4·8 (2·7–6·2)	n.s.
Mean percentage of repetitive waves	92 (0–100)	0 (0–20)	<0·01
Mean percentage of tertiary waves	100 (100–100)	100 (11–100)	n.s.
Middle third of oesophageal body			
Mean amplitude of contractile waves (mmHg)	61·0 (33·2–162·0)	25·8 (14·5–91·9)	<0·01
Mean duration of contractile waves (s)	3·6 (2·4–6·0)	3·3 (1·6–6·1)	n.s.
Mean percentage of repetitive waves	79 (0–100)	0 (0–16)	<0·01
Mean percentage of tertiary waves	100 (100–100)	100 (20–100)	<0·05
Upper third of oesophageal body			
Mean amplitude of contractile waves (mmHg)	32·5 (18–121)	22 (12–95)	<0·05
Mean duration of contractile waves (s)	2·4 (1·6–6·2)	2·1 (1·6–5·5)	n.s.
Mean percentage of repetitive waves	69 (0–100)	0 (0–28)	<0·05
Mean percentage of tertiary waves	100 (100–100)	18 (0–100)	<0·01

Values are median (range). *Wilcoxon rank sum test for paired data; n.s., not significant pressure waves of normal or above-normal amplitude, which were often repetitive. Some 10 years later, Sanderson *et al.*[2], using manometric criteria, selected a group of patients and established that, apart from dysphagia and regurgitation, thoracic pain was an important symptom and was associated with a marked pattern of abnormal contractility and reduced oesophageal dilatation. Since then, the definition of this variety of achalasia, based fundamentally on manometric findings, has varied with different authors[3-5,7]. This has recently led to some[8,9] questioning the validity of vigorous achalasia as a clinical syndrome distinct from the idiopathic form. Todorczuk *et al.*[9] established three subgroups of patients with achalasia based on amplitude of deglutition waves. They found no significant clinical differences in these groups. Likewise, Goldenberg *et al.*[8], who classified patients into two subgroups (typical and vigorous achalasia) using the same criteria as Todorczuk *et al.*[9], found that clinical and radiological data and certain manometric results (proportion of repetitive waves) were very similar in both forms of achalasia, and concluded that the distinction of 'vigorous' and 'non-vigorous' subsets based on mean amplitude alone is arbitrary, of little clinical importance and should possibly be abandoned.

From a therapeutic viewpoint, some authors have reported that vigorous achalasia has a poorer response to dilatation than the typical form[2,3] and have recommended surgical treatment. A thoracic approach allows the myotomy to be extended, if so desired, further on to the body of the oesophagus to the point where there are excess pressure and/or repetitive waves[10-12]. However, the therapeutic response to dilatation has recently been reported to be good and similar to that obtained in typical achalasia[13,14]. The present results show that Heller's myotomy, not extended to the oesophageal body and performed via an abdominal approach, achieves good or excellent clinical results in 100 per cent of patients with vigorous achalasia, similar to results obtained in typical achalasia. Likewise, postoperative manometry showed that suppression of the 'barrier' effect at the LOS causes a significant decrease in the amplitude of tertiary waves in the oesophageal body, together with the almost total disappearance of repetitive waves.

The present results suggest that in vigorous achalasia the motor alterations of the oesophageal body may be partly connected with the barrier effect produced at the LOS. The authors, like others[8,9], question the use of the term vigorous achalasia, not only from a clinical and radiological viewpoint but also from a therapeutic perspective.

Acknowledgements

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Granulocyte–macrophage colony-stimulating factor inhibits tumour growth

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The effect of granulocyte–macrophage colony-stimulating factor (GM–CSF) on murine antitumour responses was examined. Sixty mice received Lewis lung carcinoma implants and were then randomized to receive GM–CSF 1 μg/day, GM–CSF 0·5 μg/day or saline for 10 days and studied with regard to tumour volume, carcass weight and food intake. Macrophage antitumour mechanisms including oxygen free radical production and nitric oxide release were studied in peritoneal macrophages after co-culture with GM–CSF in vitro *and* in vivo. *GM–CSF 1 μg/day decreased tumour growth after 5 days (mean(s.e.m.) 0·62(0·14)* versus *1·24(0·19) cm*^{3}, $P = 0·017$*). GM–CSF upregulated macrophage antitumour mechanisms by enhancing the* in vivo *production of superoxide radicals (mean(s.e.m.) 0·69(0·06)* versus *0·45(0·10) nmol,* $P < 0·05$*) and nitric oxide (mean(s.e.m.) 48(3)* versus *24(4) μmol,* $P < 0·01$*). GM–CSF functions through the enhancement of macrophage tumoricidal activity, suggesting a therapeutic potential for this cytokine in the tumour-bearing host.*

The immune system plays a pivotal role in the host response to disease and recent anticancer therapy has been directed at modulation of components of this system. Cytokine immunotherapy regulates antitumour defence mechanisms and may be beneficial as a form of immunotherapy. The cytokine granulocyte–macrophage colony-stimulating factor (GM–CSF) is a glycoprotein of molecular mass 14 kDa secreted by activated T cells, endothelial cells, fibroblasts and macrophages[1].

GM–CSF supports proliferation of bone marrow-derived progenitors of granulocytes and macrophages, and regulates the development of these early haematopoietic progenitor cells. Phase I and II clinical trials currently under way indicate that GM–CSF may be effective in accelerating the recovery of patients with leukaemia after autologous bone marrow transplantation[2]. GM–CSF is also of benefit to patients with myelodysplastic syndrome[3]. Neutropenic patients with acquired immune deficiency syndrome receiving daily doses of GM–CSF for 14 days exhibited marked leucocytosis[4], and patients with inoperable metastatic sarcoma receiving doxorubicin, ifosfamide and dacarbazine experienced a reduction in the duration and degree of neutropenia when treated with this cytokine[5].

Although GM–CSF has an established myelopoietic activity, its role as an antineoplastic agent awaits further evaluation. An important pathway in antitumour defence may be provided by GM–CSF as it induces macrophage tumoricidal activity *in vitro*[6] and is capable of stimulating antibody-dependent cytolysis of tumour cells by mature human neutrophils and eosinophils[7]. The present study evaluated the *in vitro* and *in vivo* antineoplastic effects of GM–CSF in a murine carcinoma model.

Materials and methods

Reagents

Endotoxin (lipopolysaccharide (LPS) from *Escherichia coli* serotype 055:B5), superoxide dismutase and cytochrome *c* type III were obtained from Sigma Chemicals, Poole, UK. Cytochrome *c* was stored at −20°C in Krebs–Ringer phosphate dextrose (KRPD). Dulbecco's modified Eagles medium (DMEM) and all chemicals used for making KRPD and phosphate-buffered saline (PBS) were purchased from Life Technologies, Paisley, UK. Purified recombinant murine GM–CSF with a specific activity in excess of 1×10^5 units/mg was a gift from Dr Stephen Gillis, Immunex, Seattle, Washington, USA. All solutions were free from detectable LPS as tested by *Limulus* amoebocyte assay (E-toxate; Sigma).

In vivo *tumour studies*

Female C57/Bl6j mice (H_2D) (6–8 weeks old; $n = 60$ – Charles River Laboratories, Margate, UK) were studied. Animals were fed standard rodent chow, and after a 7-day acclimatization period were weighed and administered 10^6 Lewis lung carcinoma cells (LL/2, CRL, 1642; ATCC, Rockville, Maryland, USA) subcutaneously in the right flank. All mice developed palpable tumours 7–10 days after inoculation. At 14 days after inoculation, when the mean tumour volume was 0·4 cm^3, mice were randomized to receive intraperitoneal injections of either GM–CSF for 10 days at a dose of 1 μg/day ($n = 22$) or 0·5 μg/day ($n = 24$), or saline vehicle control ($n = 14$). These doses were based on pilot studies assessing dose-related toxicity. All mice were killed 21 days after the start of treatment.

In vivo *cytotoxicity studies*

Female CD-1 mice (6–8 weeks old; $n = 16$) (Charles River Laboratories) were randomized to receive intraperitoneally either GM–CSF 0·5 μg/day ($n = 7$) or saline vehicle control ($n = 9$) for 5 consecutive days. Animals were then killed and peritoneal cells harvested for assessment of antitumour activity.

In vitro *cytotoxicity studies*

Peritoneal macrophages from normal 6–8-week-old female CD-1 mice ($n = 30$) were co-cultured in DMEM with or without GM–CSF 50 ng/ml for 24 h (superoxide radical) or 72 h (nitric oxide) before *in vitro* cytotoxicity assays.

Assessment of tumour volume, carcass weight and food intake

Tumour volume (V) was assessed according to the equation:

$$V = (\pi/6) \times L \times S^2$$

where L is the longest dimension and S the shortest. Measurements were made immediately before treatment and at 5, 10, 15 and 20 days afterwards. All measurements were carried out using callipers by an observer who was unaware of the treatment group.

Carcass weight was calculated by subtracting tumour weight from total body-weight. Food intake was measured each day.

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Isolation of peritoneal cells

Peritoneal macrophages were harvested by peritoneal lavage with 7–10 ml LPS-free PBS as previously described[8]. Macrophages were plated at a concentration of 1×10^6 cells/ml and allowed to adhere for 2 h before study.

Assay of superoxide radical generation

Superoxide anion generation was measured as the superoxide dismutase-inhibitable reduction of ferricytochrome *c*, using phorbol myristate acetate (PMA; 1 μg/ml) as a stimulus[8]. Results are expressed as nmoles of oxygen free radical per 2×10^5 cells plated per 90 min.

Assay of nitric oxide release

Nitric oxide was determined by measuring the stable end-product nitrite[9] after 72 h incubation of macrophages with LPS (1 μg/ml) and GM-CSF (50 ng/ml for *in vitro* studies).

Macrophage phagocytosis of tumour cells

Peritoneal macrophages from CD-1 mice ($n = 8$) were plated (2×10^5 cells/well) in Labtek tissue culture slides (Nunc, Naperville, Illinois, USA). After 2 h adherence, macrophages were cultured in DMEM for a further 24 h with or without GM-CSF 50 ng/ml. Macrophage phagocytosis of Lewis lung carcinoma cells was determined by co-culturing tumour cells with macrophages (tumour cell:macrophage ratio 4:1) for 1 or 3 h. After incubation, wells were washed twice with PBS to remove non-phagocytosed tumour cells. Macrophage phagocytosis of tumour cells was assessed by counting the number of macrophages that had completely phagocytosed one or more tumour cells after 1 or 3 h. Data are expressed as the percentage of macrophages ingesting one or more tumour cells; at least 200 macrophages were counted per slide. All experiments were performed a minimum of three and some up to five times. The Lewis lung cell line was maintained in an albumin-enriched DMEM culture medium; cell culture flasks were split twice weekly. The immunogenicity of the tumour did not vary throughout the study.

Effect of GM-CSF on different cell populations

Peritoneal cell harvests were obtained from mice treated *in vivo* with GM-CSF 0·5 μg/day or saline vehicle control for 5 days, and assessed for cell yield and percentage of resident peritoneal macrophages and neutrophils, using a Romanofsky stain.

Direct effect of GM-CSF on tumour cell proliferation

Lewis lung carcinoma cells (1×10^6/ml) were cultured in 5 ml DMEM with or without GM-CSF 50 ng/ml. After 24 h, the tumour cells were removed from the culture flasks using trypsin-ethylene diamine tetra-acetic acid and counted with a haemocytometer. The direct effect of GM-CSF on tumour cell proliferation was assessed by comparing the number of tumour cells that were co-cultured with GM-CSF with those that were cultured in medium alone.

Tumour histology

Tumour specimens were fixed in formalin and stained with haematoxylin and eosin. Specimens were examined for the presence of inflammatory cells from both control and GM-CSF-treated animals killed on days 6, 9 and 12.

Statistical analysis

Assays were performed on pooled peritoneal macrophages using three to five mice for each assay. Data are presented as mean(s.e.m.). Statistical analysis was performed using Student's unpaired *t* test for comparison of two groups and analysis of variance for more than two groups. Significance was determined at $P < 0{\cdot}05$.

Results

Tumour volume, carcass weight and food intake

As shown in *Figure 1*, administration of GM-CSF 1 μg/day was associated with a significant ($P = 0{\cdot}017$) decrease in tumour volume at day 5 and throughout the 20-day study period. At a dose of 0·5 μg/day the reduction in tumour volume became significant ($P = 0{\cdot}038$) only at 19 days.

There was a mean(s.e.m.) 14·6(3·7) per cent reduction in carcass weight in the control group at day 10; this was significant compared with treated mice. The percentage changes in carcass weight did not remain significant at day 20 (*Figure 2*).

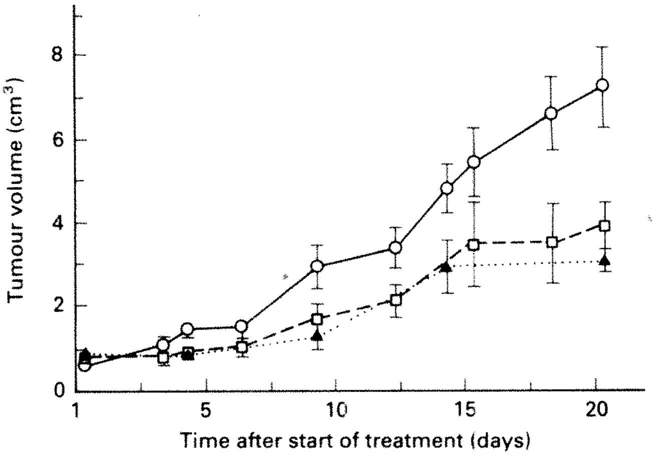

Figure 1 *Effect of granulocyte–macrophage colony-stimulating factor (GM-CSF) on tumour volume. Values are mean(s.e.m.).* ○, *Controls;* □, *GM-CSF 0·5 μg/day;* ▲, *GM-CSF 1 μg/day*

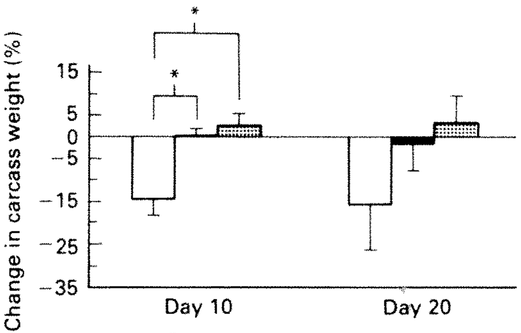

Figure 2 *Effect of granulocyte–macrophage colony-stimulating factor (GM-CSF) on carcass weight. Values are mean(s.e.m.).* □, *Controls;* ■, *GM-CSF 1 μg/day;* ▨, *GM-CSF 0·5 μg/day.* **P < 0·05 (Student's t test)*

There was no significant alteration in food intake during the study period in any group (data not shown).

Macrophage antitumour mechanisms – superoxide radical production

PMA-stimulated superoxide anion production was significantly ($P < 0{\cdot}01$) increased compared with controls in peritoneal macrophages from CD-1 mice co-cultured *in vitro* with GM-CSF (*Figure 3a*).

In vivo administration of GM-CSF upregulated PMA-stimulated superoxide radical release from peritoneal macrophages harvested from CD-1 mice after 5 days (*Figure 3b*).

Macrophage antitumour mechanisms – nitric oxide release

Nitric oxide, the tumoristatic product of L-arginine metabolism, was released from peritoneal macrophages in significantly ($P < 0{\cdot}01$) higher amounts after co-culture with GM-CSF (*Figure 4a*).

In vivo administration of GM-CSF also caused a significant ($P < 0{\cdot}01$) upregulation in generation of nitric oxide when peritoneal macrophages were co-cultured with LPS 1 μg/ml for 72 h (*Figure 4b*).

Peritoneal cell response to GM-CSF

In vivo administration of GM-CSF 20 μg per kg body-weight for 5 days was associated with a significant increase in mean(s.e.m.) peritoneal cell yield ($10{\cdot}3(1{\cdot}0) \times 10^6$ for controls *versus* $17{\cdot}9(0{\cdot}1) \times 10^6$ for GM-CSF, $P < 0{\cdot}02$) and a significant influx of neutrophils into the peritoneal cavity (8·5(0·5) *versus* 17·5(1·0) per cent, $P < 0{\cdot}02$). There was no

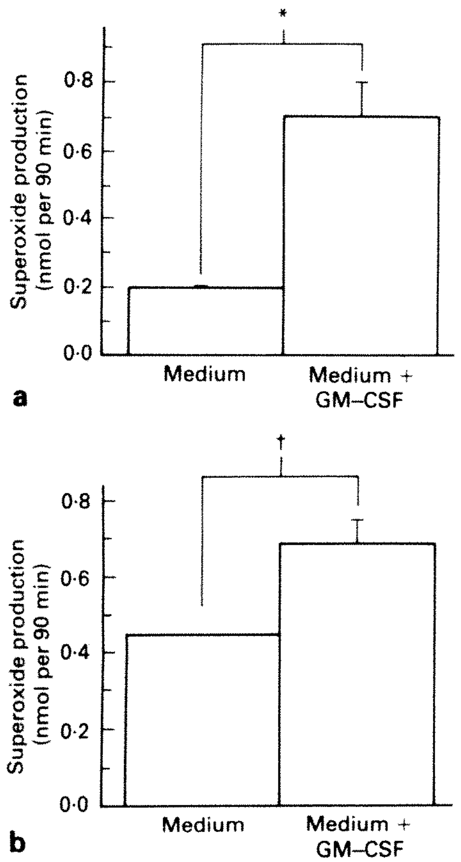

Figure 3 *Effect of granulocyte–macrophage colony-stimulating factor (GM–CSF) on superoxide radical production* **a** in vitro *and* **b** in vivo. *Values are mean(s.e.m.).* *P < 0·01, †P < 0·05 (*Student's* t *test*)

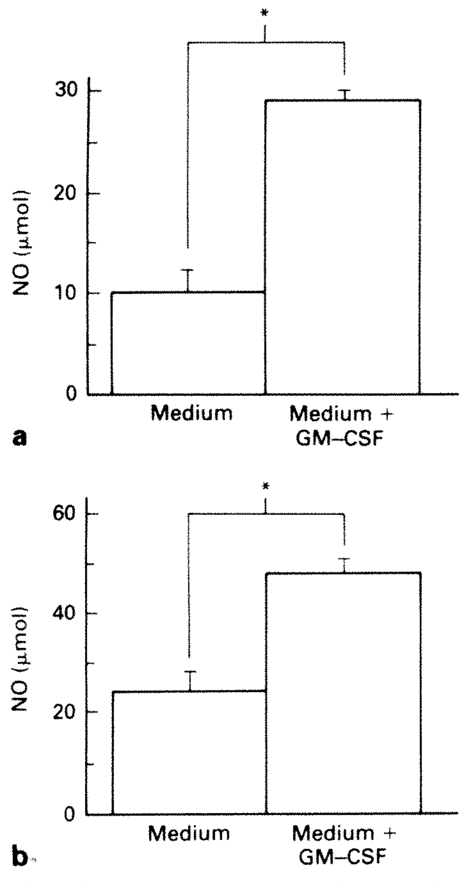

Figure 4 *Effect of granulocyte–macrophage colony-stimulating factor (GM–CSF) on nitric oxide (NO) release* **a** in vitro *and* **b** in vivo. *Values are mean(s.e.m.).* *P < 0·01 (*Student's* t *test*)

significant difference in the proportion of peritoneal macrophages in the GM–CSF-treated group (45(1) per cent for controls *versus* 47(2) per cent for GM–CSF).

Macrophage phagocytosis of tumour cells

Co-culture of macrophages and tumour cells in medium alone and in medium with GM–CSF 50 ng/ml for either 1 or 3 h revealed no evidence of direct ingestion of tumour cells by macrophages.

Direct effect of GM–CSF on tumour cell proliferation

GM–CSF caused no direct enhancement of tumour cell proliferation. After 24 h culture in 5 ml DMEM, 1×10^6 tumour cells increased in number to $3{\cdot}85 \times 10^6$, whereas 24 h of culture in 5 ml DMEM with GM–CSF 50 ng/ml increased the tumour cell count to $3{\cdot}87 \times 10^6$ (*P* not significant).

Percentage cell influx into tumours

No significant influx of inflammatory cells was revealed in either the control or GM–CSF-treated tumour specimens by standard haematoxylin and eosin staining. Areas of necrosis within the tumour specimen showed an influx of inflammatory cells.

Discussion

Cytokines implicated for use in cancer therapy include the interleukins, the interferons, tumour necrosis factor[10,11] and the colony-stimulating factors[12]. Cytokines are capable of producing significant and sustained responses against a number of tumours. Clinically, the highest response rates to cytokine immunotherapy have been seen in patients with melanoma and renal cell cancer[13].

In the present study, GM–CSF at 1 and 0·5 μg/day was associated with a significant reduction in tumour volume. The reduction in carcass weight was significantly greater after 10 days in control mice than in those that had received GM–CSF, suggesting that this cytokine may be important in regulating metabolic processes such as the cachectic response in tumour-bearing animals. No significant alteration in food intake was noted between the groups.

GM–CSF caused an increase in the release of the tumoricidal superoxide anion from peritoneal macrophages both *in vitro* and *in vivo*. To date, interferon (IFN) γ is the only cytokine that fulfils the criteria of a macrophage-activating factor[14]; however, the present experiments indicate that GM–CSF has potent macrophage-activating properties. IFN-γ and GM–CSF may function through similar pathways.

Nitric oxide production has been identified in a large number of mammalian cells[15]. Activation of the deiminase pathway has been implicated in macrophage-mediated tumoristatic[9] and microbicidal[16,17] mechanisms and may also play a role in regulating macrophage activation[18]. Release of nitric oxide, the tumoristatic product of L-arginine metabolism, was significantly upregulated by GM–CSF *in vitro* and *in vivo*. This is another mechanism through which GM–CSF may enhance macrophage cytotoxicity against tumour cells.

The mechanism of inhibition of tumour growth by GM–CSF remains unclear. The cytokine appears to have no direct action on tumour cell proliferation as no significant effect on proliferation was caused by co-culturing tumour cells with GM–CSF. Although macrophage-mediated mechanisms appear important in reducing tumour growth, no evidence of direct ingestion of tumour cells by macrophages was demonstrated.

No histological evidence was found of increased macrophage infiltration in GM–CSF-treated mice. Peritoneal cell harvests from animals treated with GM–CSF *in vivo* revealed no increase in the proportion of macrophages. These data support the theory that inhibition of tumour growth by GM–CSF results from activation of tumour-associated macrophages by this cytokine with enhanced release of superoxide anion and nitric oxide, rather than from an increase in macrophage infiltration of the tumour.

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Announcement

Frontiers and Perspectives of Surgical Oncology

A tripartite meeting of the European Society of Surgical Oncology, British Association of Surgical Oncology and the Oncology Section of the German Society of Surgery will take place on 8-11 June 1994 in Heidelberg, Germany. The meeting, Frontiers and Perspectives of Surgical Oncology, is the idea of leading surgical oncologists from the European Society of Surgical Oncology and will provide a unique opportunity for exchange of ideas and information between members of national and European societies. The scientific programme reflects the clinical relevance and increasing importance of surgical oncology. This will be the largest convention of surgical oncologists ever to have met in Europe. The official language of the meeting is English. For further details contact: Dr Thomas Lehnert, Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, D-69120 Heidelberg, Germany. Telephone: +49 6221 566207. Facsimile: +49 565450.

Christian Herfarth
Congress President

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Role of surgery and chemotherapy for peripheral lymph node tuberculosis

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A total of 105 patients with peripheral lymph node tuberculosis were treated by either surgical excision and chemotherapy or chemotherapy alone. The cervical nodes were affected in 98 patients, axillary nodes in four and inguinal nodes in three. Biopsy of the lymph nodes confirmed the diagnosis in all cases. Thirty-five patients who had sinus, ulcer or abscess underwent excision of the lymph nodes with drainage of the abscess, or resection of the sinus or ulcer. The remaining 70 patients received only chemotherapy. Chemotherapy in all patients consisted of isoniazid and ethambutol for 18 months. Of the 35 patients treated with surgery and chemotherapy, two had gaping wounds, one infection and one cellulitis of the face and neck. After 3 months, one patient had recurrence of the lymph node mass and one recurrence of a sinus; these were excised. Of the 70 patients treated only with chemotherapy, 13 were lost to follow-up. Four had non-healing wounds at the biopsy site, six wound infection and two sinus formation. Five of these patients had persistent lymph node masses, which were excised after 3 months. The remaining 52 patients had no recurrence.

The diagnosis and management of peripheral lymph node tuberculosis remain major problems in most countries of Asia and Africa. The disease frequently involves the lymph nodes draining the head and neck[1]. There are many types of management, each having its own advocates. Surgery with chemotherapy and chemotherapy alone have been tried with varying results[2–7].

On the basis of specific indications, patients in the present study were treated by either surgery with chemotherapy or chemotherapy alone. The results are reported.

Patients and methods

A total of 105 patients with peripheral lymph node tuberculosis treated between January 1988 and July 1989 formed the study group. All patients underwent biopsy of a peripheral lymph node for histological analysis. A diagnosis of lymph node tuberculosis was based on the following histopathological findings: caseating type, consisting of central caseation necrosis, surrounded by epithelioid cells, lymphocytes and Langhans' giant cells; and lymphadenoid type, without caseation necrosis and consisting of reticuloendothelial hyperplasia, with sheets of epithelioid cells and irregular arrangements of Langhans' giant cells. The nodes were not subjected to microbiological examination. Other investigations included estimation of the erythrocyte sedimentation rate (ESR) and chest radiography.

Patients were divided into two groups: those with complications such as ulcer, abscess or sinus ($n = 35$) and those without complications ($n = 70$). Patients with complications were treated by surgery, i.e. lymph node excision with resection of an ulcer or sinus, or drainage of an abscess, and chemotherapy. All 105 patients were treated with oral isoniazid 15 mg per kg body-weight and ethambutol 25 mg/kg as a single daily dose for 18 months. Patients without complications were given chemotherapy alone.

The size of the lymph nodes was measured at the beginning of treatment and patients were followed at intervals of 3 months. Those who did not respond to drugs underwent excision of the nodes after 3 months. A node was considered to have disappeared when its diameter was <5 mm. Patients were encouraged to continue drug treatment and followed to 18 months to assess progress, as evidenced by improvement of general symptoms, weight gain, regression of lymph nodes and a decreasing ESR.

Results

Of the 105 patients, the youngest was 1·5 and the oldest 68 years of age; 78 patients were between 11 and 30 years old. The male:female ratio was 1:1·3 (*Table 1*). Cervical lymph nodes were affected in 98 patients, axillary nodes in four and inguinal node involvement was present in three. Of the 98 patients with cervical lymph node tuberculosis, the jugulodigastric ($n = 32$), posterior triangle ($n = 28$), submandibular ($n = 19$), submental ($n = 7$), supraclavicular ($n = 10$), preauricular ($n = 1$) and postauricular ($n = 1$) nodes were involved. Clinical evidence of matting of nodes was found in 71 patients (68 per cent) and in 34 patients (32 per cent) the nodes were discrete. The mean node diameter was 19 (range 17–28) mm. Weight loss was noted in 78 per cent of patients, fever in 45 per cent and night sweats in 35 per cent. Pulmonary tuberculosis was detected on chest radiography in 17 patients. One had diabetes mellitus. Six had a positive history of a family member suffering from pulmonary or extrapulmonary tuberculosis. The diagnosis was confirmed by histopathological analysis. The ESR was increased in all patients and ranged from 21 to 60 mm/h.

Thirty-five patients had complications: 16 had abscesses, 11

Table 1 *Age and sex of 105 patients with peripheral lymph node tuberculosis*

Age group (years)	No. of patients	
	M	F
0–10	4	5
11–20	19	27
21–30	13	19
31–40	3	2
41–50	4	3
51–60	2	2
61–70	1	1
Total	46	59

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Table 2 *Results of treatment in 105 patients with peripheral lymph node tuberculosis*

Patients treated with surgery and chemotherapy ($n = 35$)	
Cosmetically acceptable scars, good response	33
Recurrence of sinus (re-excision performed)	1
Recurrence of lymph nodes (re-excision performed)	1
Complications	
Non-healing wound	2
Wound infection	1
Cellulitis of face and neck	1
Patients treated only with chemotherapy ($n = 70$)	
Lost to follow-up	13
Good response	52
Persistent lymph node masses (excision performed)	5
Complications	
Non-healing wound	4
Wound infection	6
Sinus formation	2

The two groups were not significantly different (χ^2 test)

sinuses and eight ulcers. The other group ($n = 70$) had palpable lymph nodes only. After the diagnosis was confirmed, patients with complications underwent excision of lymph nodes, drainage of abscesses, and resection of sinuses or ulcers as appropriate. Those without complications were managed only with chemotherapy.

Response to treatment in both groups and the rate of complications are given in *Table 2*. Non-healing of wounds, wound infections and cellulitis of the face followed node biopsy. In patients of both groups, non-healing wounds and other complications responded well to chemotherapy. In the group undergoing surgery, wounds healed well with cosmetically acceptable scars. One patient had recurrence of a sinus after 3 months and one palpable nodes 15 mm in diameter; these were excised. In the group treated only with chemotherapy, 13 patients were lost to follow-up; of the remaining 57, five had persistent lymph node masses (mean diameter 14 mm), which were excised at the end of 3 months. Nodes disappeared in 52 patients.

Results were analysed using the χ^2 test; the two groups did not differ significantly. The difference in the rate of complications was also found not to be significantly different in both groups. Patients with a good response had weight gain, were symptom-free and had a decreasing ESR.

Discussion

Tuberculosis is one of the commonest diseases affecting peripheral lymph nodes. Cervical nodes are most frequently involved[4,5,7]; in the present study these nodes were involved in over 90 per cent of cases. Histopathological findings, whether indicating caseating or lymphadenoid type, are unrelated to treatment, and biopsy is always undertaken to confirm the diagnosis of tuberculosis in the Indian subcontinent[2].

Associated pulmonary lesions were found in 16 per cent of the present cases and a family history of tuberculosis in 6 per cent, suggesting that the incidence of tuberculosis has not significantly decreased in the general population.

Many treatments have been tried in the management of peripheral node tuberculosis. Surgical excision with chemotherapy, chemotherapy first and then surgery, or chemotherapy alone with antitubercular drugs for varying durations have been used[4,6,7]. Reports of the efficacy of these methods have usually been based on retrospective studies with uncontrolled data for patient selection[6,7]. The results of such studies suggest that surgery and chemotherapy, or chemotherapy alone, yield similar results[2,4,6], but in patients with sinuses and ulcers excision with chemotherapy helps to obtain a cosmetically acceptable scar[8].

In the present study both the group with complicated disease and that without achieved similar results. Surgery may be recommended for ulcers, sinuses or abscess with a view to obtaining a cosmetically acceptable scar. Although various drug regimens are available, in the present study ethambutol and isoniazid were used for 18 months as recommended by the government of India and Maharashtra[9], with good results.

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Prognostic value of DNA ploidy in primary gastric leiomyosarcoma

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The prognostic value of DNA ploidy was evaluated in 25 patients with primary gastric leiomyosarcoma, using paraffin-embedded archival specimens analysed by DNA flow cytometry. Ploidy patterns were diploid in ten tumours and non-diploid in 15. They did not correlate with clinicopathological features of the lesions such as tumour size and grade or mitotic index. A non-diploid pattern was associated with a significantly reduced patient survival rate ($P < 0.05$)*, as was higher tumour grade* ($P < 0.01$)*. Neither tumour size nor mitotic index correlated with patient survival.*

The prognosis of patients with primary gastric leiomyosarcoma has traditionally been predicted by morphological features of the lesion such as tumour size and grade, cellularity and mitotic index[1,2]. Recently, DNA ploidy patterns of tumour cells determined by flow cytometry have become accepted as indices for predicting the survival of patients with various malignant tumours[3–6].

In the present study, the ploidy of 25 primary gastric leiomyosarcomas was determined using flow cytometric techniques, in an aim to assess the prognostic value of ploidy for malignant smooth muscle tumours of the stomach.

Patients and methods

Patients

Twenty-five patients who had undergone apparently curative resection of primary gastric leiomyosarcoma between October 1975 and July 1991 were studied. The patients comprised 15 men and ten women of mean(s.d.) age 58(15) (range 20–77) years. Tumour size was defined as the largest dimension of each lesion, as obtained from medical records; it ranged from 15 to 200 mm and was greater than 50 mm in 14 tumours.

The mitotic index was determined by counting mitotic figures from the most cellular area of tumour tissue in ten consecutive high-power fields (×40 objective lens), which corresponded to 1·94 mm^2 in a section[7]. The index ranged from 0 to 80 mm^{-2} and was greater than 5·0 mm^{-2} in 16 tumours. The tumour grade, determined histopathologically according to a clinicopathological staging system for soft tissue sarcoma[8], was grade I in seven tumours, grade II in 11 and grade III in seven.

Follow-up was complete until December 1992 or death of the patient. Eighteen patients are alive and free from recurrent disease and seven have died from malignancy.

DNA flow cytometry

Two or three 50-μm sections were cut from paraffin-embedded tumour tissue. The technique of Schutte *et al.*[9] was employed for the preparation of single dissociated nuclei. The method of Vindeløv *et al.*[10] was used for staining nucleic acids with propidium iodide. The nuclear content of 20 000 cells was measured using a flow cytometer (FACScan; Becton–Dickinson, Mountain View, California, USA) and DNA histograms generated using a computer attached to the system. Stromal cells contained in tumour tissue were used as an internal standard for 2C (i.e. diploid) DNA content. The DNA index was defined as the ratio of the G0/G1 peak modal chamber number for tumour cells to the G0/G1 peak modal chamber number for diploid stromal cells. The DNA histogram was defined as diploid when tumour cells generated a single G0/G1 peak in the diploid region (DNA index 1·0), as shown in *Figure 1*. Other DNA histograms were defined as non-diploid (*Figure 2*). Samples with G0/G1 peaks with a coefficient of variation greater than 8 per cent were excluded.

Statistical analysis

χ^2 test with Yates' correction was used for determining the significance of correlation between each variable. Cumulative survival rates were obtained using the Kaplan–Meier method. The significance of the difference in survival rates between each group of patients was determined by the log rank test. $P < 0.05$ was considered significant.

Results

The mean(s.d.) coefficient of variation of the G0/G1 peaks of 25 tumour tissue samples was 4·9(2·0) per cent. Non-diploid DNA patterns were detected in 15 of 25 tumours. The DNA index ranged from 0·59 to 2·01. There was no significant correlation between DNA ploidy and clinicopathological features of primary gastric leiomyosarcoma (*Table 1*).

The non-diploid DNA patterns of tumour cells were associated with a significantly reduced patient survival rate ($P < 0.05$; *Figure 3*), as was higher tumour grade ($P < 0.01$; *Figure 4*). On the other hand, there were no significant effects

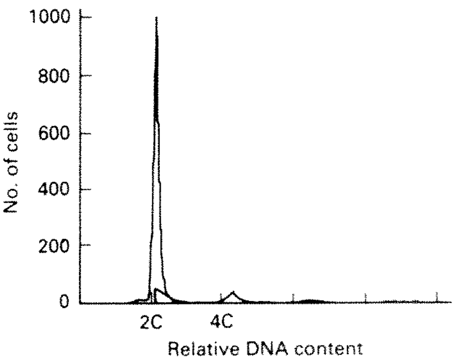

Figure 1 *Exemplary diploid DNA histogram of primary gastric leiomyosarcoma*

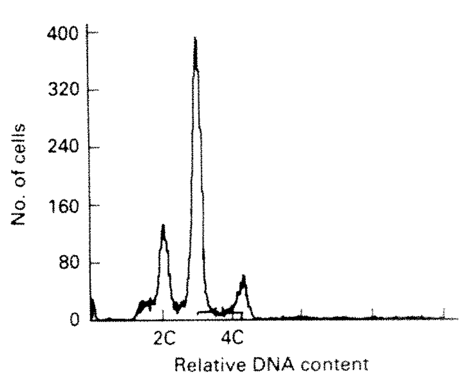

Figure 2 *Exemplary non-diploid DNA histogram of primary gastric leiomyosarcoma*

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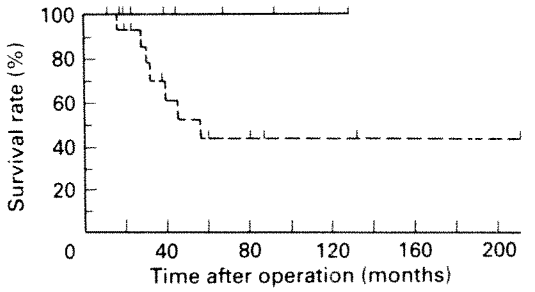
Table 1 *DNA ploidy and clinicopathological features of 25 primary gastric leiomyosarcomas*

	Diploid ($n = 10$)	Non-diploid ($n = 15$)	P*
Sex ratio (M:F)	6:4	9:6	0·66
Age (years)			
>40	9	12	0·47
⩽40	1	3	
Tumour size (mm)			
>50	6	8	0·53
⩽50	4	7	
Mitotic index (mm^{-2})			
>5·0	5	11	0·22
⩽5·0	5	4	
Tumour grade			
I	4	3	0·52
II	4	7	
III	2	5	

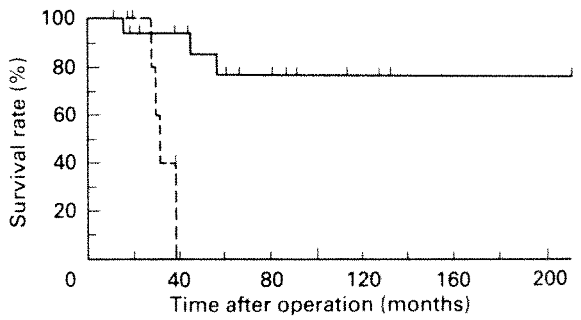
*χ^2 test



No. at risk

Diploid	10	10	10	10	–	–
Non-diploid	15	7	4	3	1	1

Figure 3 *Effect of DNA ploidy pattern on the survival of patients with primary gastric leiomyosarcoma. ——, Diploid pattern; – – –, non-diploid pattern; ⊥, survivor. Non-diploid DNA patterns were associated with a significantly reduced survival rate (P < 0·05, log rank test)*



No. at risk

Grade I/II	18	12	7	3	1	1
Grade III	7	0	–	–	–	–

Figure 4 *Effect of tumour grade on the survival of patients with primary gastric leiomyosarcoma. ——, Grade I or II; – – –, grade III; ⊥, survivor. The higher tumour grade (grade III) was associated with a significantly reduced survival rate (P < 0·01, log rank test)*

of larger tumour size (greater than 50 mm; $P = 0{\cdot}16$) or higher mitotic index (greater than 5·0 mm^{-2}; $P = 0{\cdot}07$) on survival.

Discussion

Morphological features such as tumour size and grade, cellularity[11] and mitotic index[12] have been recognized as markers indicating the biological behaviour of malignant smooth muscle tumours. However, these conventional pathological variables have often been defined arbitrarily and determined subjectively. Recently, DNA patterns of tumour cells, determined by flow cytometric techniques, have been recognized as accurate, objective and easily reproducible markers for predicting the prognosis of patients with a malignant tumour[3–6].

DNA flow cytometric analysis of primary gastric leiomyosarcoma has been reported by others[13,14]. In the present study, non-diploid patterns were found in 15 of 25 primary gastric leiomyosarcomas, in accord with previous reports that 50–60 per cent of such tumours had non-diploid DNA patterns[13,14].

Tsushima *et al.*[13] reported that there was a close correlation between DNA ploidy and tumour grade, but such an association was not found in the present study. The different results may reflect differences in the grading system employed: Tsushima *et al.*[13] did not describe the system they used for grading gastric leiomyosarcoma. The present study showed no significant correlation between DNA ploidy and morphological features of the tumour such as size and grade or mitotic index. This suggests that the DNA ploidy pattern of tumour cells may be useful as an independent prognostic variable for malignant smooth muscle tumours of the stomach.

The present study has confirmed previous reports[13,14] that non-diploid patterns of tumour cells are associated with a significantly reduced patient survival rate.

In conclusion, DNA ploidy, together with tumour grade, is significantly correlated with the survival of patients with this relatively rare malignant lesion. However, further studies on a larger patient population are necessary to determine whether the ploidy pattern of tumour cells may be used as a prognostic marker for primary gastric sarcoma, independent from conventional prognostic variables.

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Short note

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Raised serum CA125 level in leiomyoma and leiomyosarcoma of gastrointestinal origin

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CA125 is a serum antigen used as a marker for epithelial ovarian carcinoma. Its level is raised in some other gynaecological conditions and a few gastrointestinal carcinomas. Leiomyoma and leiomyosarcoma are stromal tumours. When they originate from the gastrointestinal tract, these tumours exhibit a wide variability in clinical behaviour. Once the tumour has been resected, subsequent follow-up relies on outpatient examination, endoscopy and imaging techniques. A serum marker for such tumours could simplify the follow-up of these patients.

Case reports

Patient 1

A previously well 61-year-old woman was admitted with a 1-week history of abdominal pain. Examination revealed a smooth firm mass arising out of the pelvis. Ultrasonography demonstrated a mainly solid mass, probably of ovarian origin. The serum CA125 level was raised at 194 units/ml (normal below 35 units/ml).

At laparotomy, a solid mass with cystic areas was found within the ileal mesentery, close to the bowel wall. The mass was resected and no other abnormalities were found.

The patient made an uneventful recovery and 4 months after operation, with no detectable recurrence, the serum CA125 level had dropped to 9 units/ml. Histological examination showed a leiomyoma without mitoses. Immunohistochemical analysis performed 6 months after resection showed no CA125 antigen expressed on the cells of the tumour.

Patient 2

A 60-year-old woman, previously fit, was admitted with a 12-h history of epigastric pain and vomiting. Physical examination revealed generalized peritonitis; urgent laparotomy was arranged.

Free intraperitoneal pus was found and a perforated tumour in the upper jejunum identified. Two solid masses were palpable in the right lobe of the liver. The tumour was resected; histological analysis showed a low-grade leiomyosarcoma.

Postoperative ultrasonography confirmed multiple hepatic metastases. Some 11 days after operation the serum CA125 level was raised at 107 units/ml.

Discussion

CA125 is the antigenic determinant identified by a murine monoclonal antibody raised specifically against epithelial ovarian carcinoma. The radioimmunoassay for serum CA125 has a high specificity in these patients[1], hence its widespread use as a serum tumour marker.

A raised serum CA125 level has been found in patients with advanced endometriosis[2], pancreatic carcinoma, cancer of the biliary tree and hepatocellular carcinoma[3]. These pathologies are of epithelial origin, although CA125 has also been demonstrated in patients with uterine leiomyosarcoma[4]. In addition, a few healthy women under 49 years of age have raised levels, as do those in early pregnancy[5]. There have been no previous reports linking a raised serum CA125 level with stromal tumours of gastrointestinal origin.

Leiomyoma and leiomyosarcoma of gastrointestinal origin are well known for their wide variability in clinical behaviour. Leiomyoma and leiomyosarcoma are the commonest stromal tumours of the stomach, although the division between the two histological entities is not clear cut. Both tumours occur less commonly elsewhere in the gastrointestinal tract. At present, surgical removal is the treatment of choice, but is not always technically possible. Follow-up of these patients consists of regular clinical review and repeated imaging investigations.

Immunohistochemical analysis was performed on tissue taken from patient 1 and there was no evidence of the CA125 antigen on the tumour cells. Thus the site of production of the serum-borne CA125 antigen is unknown and it may be produced from some distant site, stimulated by factors released by the leiomyoma. Further work is required to investigate the association between serum CA125 levels and stromal tumours of gastrointestinal origin. If this marker reflects the course of tumour growth and treatment, serum CA125 levels may prove useful in follow-up of these patients.

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Surgical workshop

Br. J. Surg. 1993, Vol. 80, December, 1552

Laparoscopic omental patch repair of perforated duodenal ulcer with an automated stapler

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Laparoscopic repair of peptic ulcer disease complicated by anterior duodenal perforation could offer a number of advantages over laparotomy[1]. Endoscopic suturing, whether extracorporeal or intracorporeal, is usually tedious and time consuming for most surgeons who perform laparoscopic procedures. Undoubtedly, this problem deters surgeons from repairing perforated duodenal ulcers in this manner. Use of an automated endoscopic stapling device (Multifire Endo-Hernia; Auto Suture, Ascot, UK) in two patients with perforated duodenal ulcer is described.

Surgical technique

Two men, aged 24 and 49 years, were admitted to hospital on an emergency basis with classical features of perforated peptic ulcer and radiological evidence of free air under the right hemidiaphragm. After initial resuscitation, laparoscopy was undertaken under general anaesthesia with full muscle relaxation. Each patient was placed in a supine position with legs apart. The surgeon stood between the legs of the patient, the first assistant on the patient's left side and the second on the right. Pneumoperitoneum was established using carbon dioxide and intraperitoneal pressure maintained at or below 15 mmHg. A 12-mm cannula was inserted at the umbilicus and used to introduce a forward-viewing laparoscope and later the endo-stapler. Under direct vision, the remaining abdominal ports were established (*Figure 1*). A 10-mm cannula in the left upper quadrant at the anterior axillary line was used to introduce an atraumatic Babcock clamp. This clamp was employed to retract the gastric antrum downwards and to the left to expose the first part of the duodenum. A 10-mm cannula to the left of the umbilical port at the mid-clavicular line enabled the introduction of the forward-viewing laparoscope. A 5-mm cannula to the right of the umbilicus allowed insertion of the grasping forceps and an optional 5-mm port was used for liver retraction.

The abdominal cavity was first explored with the laparoscope to determine the degree of peritoneal soiling and the site of perforation. Abdominal fluid was obtained for bacterial culture and sensitivity testing. The peritoneal cavity was irrigated copiously with 3 litres warm saline, ensuring that peritoneal contamination was minimized. Healthy omentum was pulled upwards towards the perforation. The endo-stapler was introduced through the 12-mm umbilical cannula and the omentum stapled to the gastric antrum, duodenum and falciform ligament (*Figure 2*). Six staples were used in each case; no attempt was made to close the perforation with the stapler. The pneumoperitoneum was desufflated and the abdominal punctures closed. The mean operating time was 18 min.

A nasogastric tube was left in place for 24 h, and both patients were discharged on day 4 after surgery.

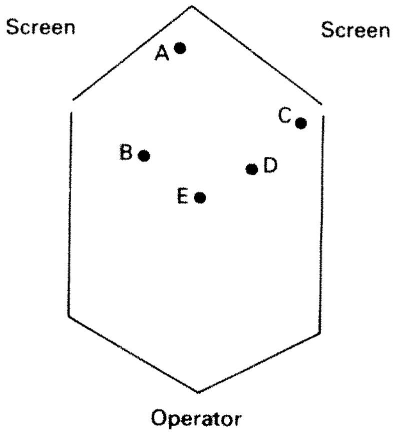

Figure 1 *Positions of the cannulas. A, liver retractor (5-mm cannula); B, grasper (5 mm); C, Babcock clamp (10 mm); D, telescope (10 mm); E, endo-stapler (12 mm)*

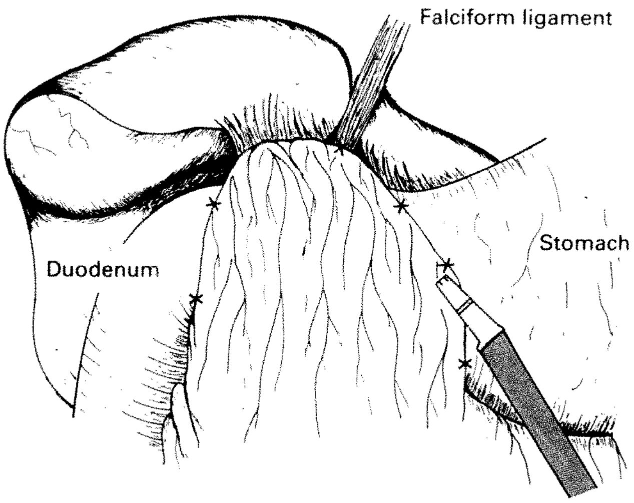

Figure 2 *Omentum stapled to the gastric antrum, duodenum and falciform ligament*

Discussion

In the authors' initial experience with six patients undergoing sutured repair of duodenal perforation[1], a technique of laparoscopic suturing and either intracorporeal or extracorporeal knot tying was adopted; this proved tedious, the mean operating time being 175 min. Use of the endo-stapler in laparoscopic repair of perforated duodenal ulcer has several advantages. First, the head of the stapler articulates enabling stapling of the omentum on to the anterior wall of the stomach; second, it greatly reduces the operating time.

With regard to the safety of the device, the staples bite only the serosa of the stomach wall rather than its full thickness. No staples are visible at endoscopy 6 weeks after operation. We believe that this preliminary study demonstrates a rapid and simple technique of laparoscopic omental patch repair of uncomplicated perforated duodenal ulcer.

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Reliability of clinical judgement in evaluation of the nutritional status of surgical patients

The ability of surgeons to make a reproducible and reliable evaluation of the nutritional status of patients was assessed. Three independent observers assigned 64 patients to one of four nutritional states – normal nourishment, and mild, moderate and severe malnutrition – using a questionnaire and clinical examination. Interobserver variability was analysed using the κ *statistic and reliability by assessing the correlation between the assigned class and total serum protein, haemoglobin, albumin, transferrin and cholesterol levels, weight loss and the results of immunological skin tests. Concordance was observed in 49 of the 64 judgements (77 per cent) and partial agreement in the remainder* ($\kappa = 0{\cdot}74$, $P < 0{\cdot}001$)*. Clinical judgement correlated significantly with albumin, transferrin and cholesterol levels and weight loss* ($R^2 = 0{\cdot}73$, $P < 0{\cdot}001$)*. Surgeons are able to assess nutritional status using clinical judgement.*

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Poorly nourished patients are more prone to develop postoperative complications and have a higher risk of mortality[1–4]. Several studies have attempted to define nutritional status in terms of anthropometric variables, laboratory assays of circulating proteins, cholesterol levels and immunological factors[5–10]. It may be assessed before surgery using mathematical formulae that contain various combinations of these measurements[10–15].

No universally accepted definition of malnutrition exists and therefore there is no 'gold standard'. The clinical judgement of the surgeon, taking into account the history, food intake, physical activity and some simple observations of muscle mass and fat deposits, might be an equally valid method.

This prospective study evaluated the reproducibility of clinical judgement in assessing nutritional status. This was compared with accepted objective tests for malnutrition. The clinical features with the greatest influence on the clinical judgement of surgeons were assessed.

Patients and methods

Patients

In total, 64 patients (33 men, 31 women; median age 62 (range 18–79) years) admitted for elective surgery entered the study. They were chosen randomly and prospectively, and constituted 20 per cent of all such patients admitted over a 3-month period. Selection was on the basis of the clinical record number; only numbers ending in 0 or 5 were chosen.

Characteristics of the study group

Table 1 shows the distribution of the patients according to age and diagnosis, compared with the total population over the same period. There were no significant differences between the two groups and the study sample can therefore be considered representative of the general population.

Objective tests

The weight of each patient was recorded at admission and compared with that measured 3 months earlier. Blood samples taken at admission were analysed for levels of albumin, haemoglobin, transferrin, total protein and cholesterol. A lymphocyte count was performed and a skin test with seven common anamnestic antigens (Multitest; Merieux, Lyon, France) carried out.

Clinical judgement

Three surgeons (one consultant, two registrars) examined each patient independently and without knowledge of the diagnosis, planned operation or results of the objective tests. They were asked to assign each patient to one of four classes: normal nourishment, and mild, moderate or severe malnutrition. These were not defined by any preset criteria. As part of the examination protocol, the observers scored specific variables shown in *Table 2* according to methods previously described[16]. No criteria were set for this scoring. The surgeons also scored their own observational assessments of the patient's adipose mass, muscle mass and conjunctival pallor on similar scales, without preset criteria.

Table 1 *Characteristics of patients*

	Study group ($n = 64$)	Total population ($n = 320$)
Median (range) age (years)	62 (18–79)	60 (18–82)
Diagnosis*		
Cancer	46 (72)	208 (65)
Benign disease	18 (28)	112 (35)

*Values in parentheses are percentages

Table 2 *Questionnaire for clinical assessment of nutritional status*

	0	5	10
Anamnestic variables			
Weight loss	High	|	None
Subjective well-being	Poor	|	Good
Working activity	Low	|	High
Appetite	Poor	|	Good
Dietary intake	Low	|	High
Partial score........			
Objective observations			
Muscle mass	|	|	|
Adipose mass	|	|	|
Sanguification	|	|	|
Partial score........			
Total score........			

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Statistical analysis

Reproducibility of clinical judgement, assessed by the degree of interobserver variation, was analysed by the κ statistic[17,18]. The value of κ varies from 0 to 1; a value of 0·4 or less indicates that chance alone can account for the observed agreement and a value of 1 perfect concordance. The statistical significance of κ and its 95 per cent confidence interval were calculated.

For correlational analysis, the nutritional status was assigned a numerical value ranging from 1 (normally nourished) to 4 (severely malnourished). For assessment of reliability, this value was taken as the dependent variable in multiple stepwise regression, with the objective assay results taken as independent variables[19]. Similarly, the eight clinical scores were taken as independent variables when assessing the contribution of each to the clinical judgement.

Differences in the distributions of the values for albumin, transferrin, cholesterol and objective weight loss among the four nutritional classes were tested by analysis of variance (ANOVA). Categorical data were analysed by the χ^2 test.

Results

Interobserver agreement

Reproducibility of clinical judgement was excellent (*Table 3*). Complete agreement was achieved in severely malnourished patients with good concordance in the normally nourished group. The greatest discordance occurred in assigning patients to mild or moderate malnutrition. Discordant results are shown in *Table 4*; in each case the disagreement was by one class.

Correlation with objective test results

No difference between the nutritional classes was present

Table 3 *Distribution of patients by level of surgeon agreement and assigned nutritional class*

	Nutritional class				
Level of agreement	Normal nutrition	Mild malnutrition	Moderate malnutrition	Severe malnutrition	Total
3 of 3	28	9	7	5	49
2 of 3	7	5	3	0	15
None	0	0	0	0	0
Total	35	14	10	5	64

$\kappa = 0{\cdot}74$ (95 per cent confidence interval 0·63–0·85) ($P < 0{\cdot}001$)

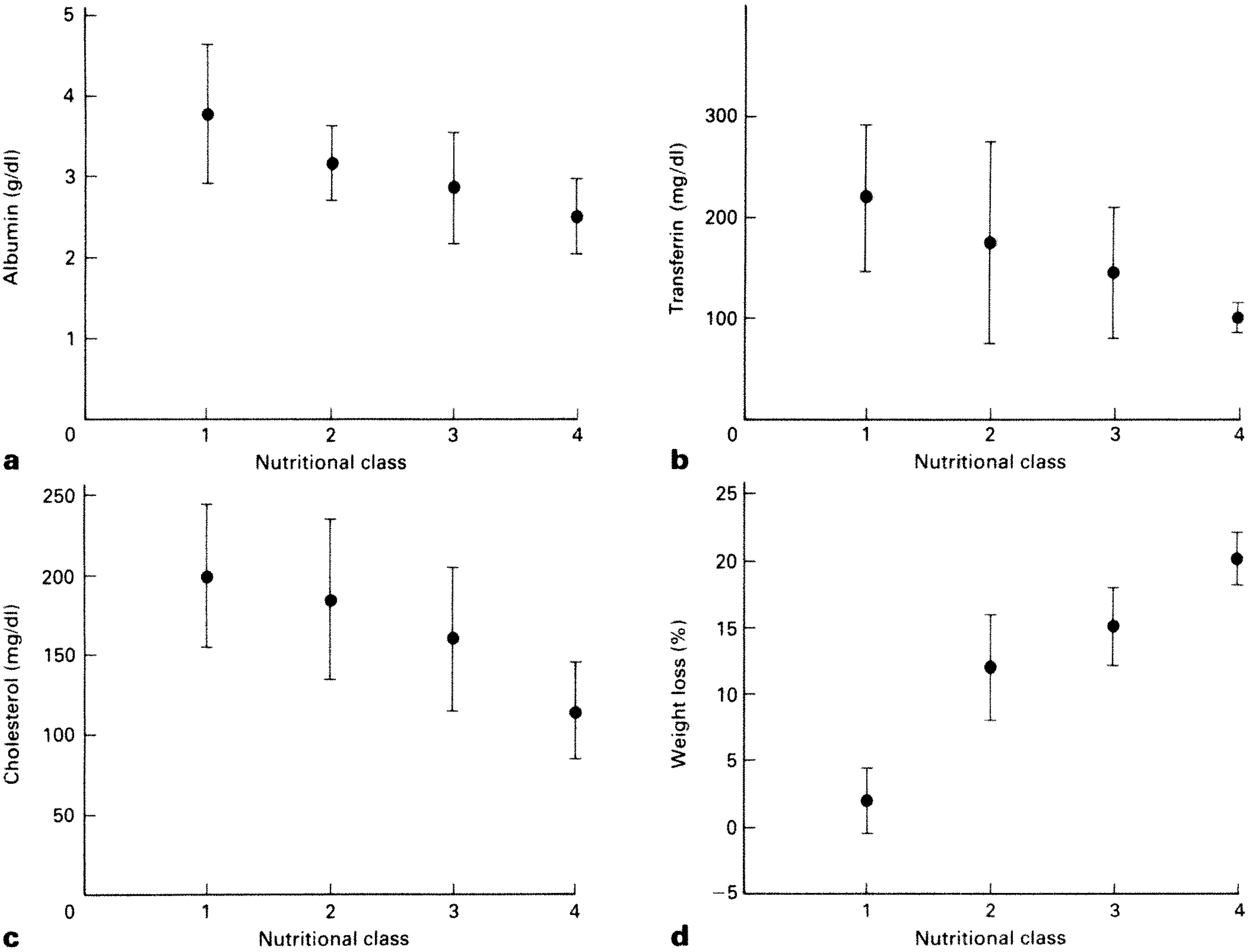

Figure 1 *Results of the four objective tests according to assigned nutritional class.* **a** *Serum albumin;* **b** *serum transferrin;* **c** *serum total cholesterol;* **d** *weight loss over a 3-month period (expressed as a percentage of initial weight). Values are mean(s.e.m.). Nutritional classes were assigned as in* Table 3

Table 4 *Distribution and quality of disagreement of the three surgeons*

	Surgeon no.			
	1	2	3	Total
No. of disagreements	3	6	6	15
Overestimation	1	3	2	6
Underestimation	2	3	4	9

regarding age distribution, or benign or malignant disease. ANOVA revealed significantly different distributions of values for objective weight loss, and albumin, transferrin and cholesterol levels between the four nutritional groups (*Figure 1*). The correlation between these variables could be expressed in the form:

$$\begin{aligned}\text{Nutritional status} = {} & 1{\cdot}78 + 1{\cdot}41 \times \text{weight loss (\%)}\\ & + 0{\cdot}019 \times \text{cholesterol (mg/dl)}\\ & - 0{\cdot}53 \times \text{albumin (g/dl)}\\ & - 0{\cdot}016 \times \text{transferrin (mg/dl)}\end{aligned}$$

This multiple regression had an R^2 value of 0·73 ($P < 0{\cdot}001$). Adding more variables did not significantly improve the correlation. Clinical judgement, therefore, correlates well with four commonly used objective parameters in the assignment of nutritional status.

Positivity to the skin tests was different in the four nutritional classes, but in the mathematical model neither this variable nor levels of serum protein and haemoglobin or lymphocyte count were found to be significant.

Clinical factors contributing to the clinical judgement

Four of the eight clinical variables were found to be strong determining factors in forming a clinical judgement. Two of these involved the patient's own assessment of well-being and weight loss, and two were observational (the observer's assessment of muscle and adipose mass). They could be fitted to an equation of the form:

$$\begin{aligned}\text{Nutritional status} = {} & 6{\cdot}109 - 5{\cdot}39 \times \text{muscle mass}\\ & - 3{\cdot}44 \times \text{adipose mass} - 0{\cdot}06 \times \text{well-being}\\ & - 0{\cdot}037 \times \text{weight loss}\end{aligned}$$

where all these variables were measured on an arbitrary scale of 0–10. The regression line had an R^2 value of 0·82 ($P < 0{\cdot}001$).

Discussion

Malnutrition has an important influence on outcome in surgical patients. There is evidence that only the severely malnourished benefit from nutritional support[20]; it is therefore important to identify these patients accurately.

Nutritional assessment is now dependent largely on the measurement of biological variables and the use of models predicting the risk of septic complications[13–15]. This approach is limited by two factors: the wide biological variability introduced by different clinical conditions such as heart, liver and renal disease, for which these measurements are unreliable, and the improper use of epidemiological models for individual estimation[21]. Shizgal[22] found that the confidence intervals of the variables usually considered are too wide to be of much value in any given patient. Measurements of total exchangeable potassium concentration[23] and neutron activation analysis[24] are not readily amenable to clinical practice. Distinctions should be drawn between methods suitable for research and those for routine clinical use, between methods for epidemiological estimation and those for evaluation of a single patient, and between techniques for group prognosis and those for recognition of malnutrition[25].

Hill[26] emphasized that 'it is time for some clinical common sense'. A valid bedside method must be simple to apply, reproducible under every condition, generally acceptable and cost–effective.

The present study shows that simple clinical examination is capable of recognizing malnutrition with a high degree of reliability and confirms the work of Baker, Detsky and colleagues[21,27]. Such judgements, although subjective and independent, are highly reproducible. No global disagreement between observers was registered. Considering that, unlike the Baker study, no training was given before the trial, no criteria were set up for the assignment of the patients to different classes and the diagnosis was deliberately withheld before formulation of the judgement, this result assumes even greater significance.

Concordance was best in the assignment of patients to the two extreme nutritional states and less complete in the two intermediate classes. Total agreement in the recognition of severely malnourished individuals is most important because these patients benefit from perioperative nutritional support[28].

Distributions of the levels of albumin, transferrin and cholesterol correlated well with clinical nutritional status but were overlapping; this makes them unsuitable for the assignment of individual patients.

Weight loss, calculated from measurements at two defined times, correlated well with clinical nutritional status and could be used to assign individuals to the correct class. This method, while practicable, is unlikely to be accurate in routine clinical practice, since the time interval between weight measurements usually varies.

The lack of correlation between nutritional classes and the skin test results can be ascribed to the multifactorial determinants of this variable. Internal analysis of data has shown that results of skin tests correlate with the presence and stage of cancer, the age of the patient and the level of serum albumin, in accordance with the findings of Twomey *et al.*[29].

The four most significant clinical variables in the formulation of clinical judgement were derived from questioning and observation of the patient. Both aspects of examination are crucial in this formulation.

This study did not consider the relationship between nutritional status and surgical outcome since variables such as type of disease, extent of surgery, technical factors, preoperative and postoperative care, and individual response to treatment were not considered[30].

Clinical evaluation of nutritional status deserves a more important role and wider use in clinical practice since it is inexpensive and easy to apply.

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Repeat hepatectomy for cancer

In a series of 279 hepatectomies performed for cancer between June 1984 and March 1992, 46 were repeat operations, for metastases in 41 patients. The primary tumour was in the colon and rectum (28 patients), APUDoma (five) and miscellaneous (eight). Repeat hepatectomies were performed in 26 per cent of patients who had recurrence after the first liver resection and in 40 per cent of those who had liver recurrence. An unsuspected extrahepatic recurrence was discovered and resected in eight instances and in two other cases a known extrahepatic recurrence was resected during the second hepatectomy. The hospital mortality rate was 2 per cent (one patient); the death was from nosocomial pneumonia. The total morbidity rate including minor complications was 32 per cent, with a higher frequency of haemorrhagic problems after secondary liver resection (12 per cent) than after primary hepatectomy (5 per cent). The rate of postoperative complications after repeat hepatectomy was related significantly to operative blood loss greater than 1500 ml (P = 0·04). The technical problems of repeat hepatectomy were: (1) re-exposure of the liver, considered to be difficult in 67 per cent of second liver resections and 80 per cent of third procedures; (2) the liver parenchyma, which often had histological modifications between first and second resections and was more difficult to 'work' as shown by the mean duration of clamping of the hepatic pedicle (54 min for secondary versus *36 min for primary liver resection); and (3) modification of the intraparenchymal vasculobiliary anatomy following liver regeneration after major hepatectomy. Intraoperative ultrasonography was of great benefit. Rates of crude and recurrence-free survival were relatively encouraging at 47 and 33 per cent 3 years after the second liver resection for the whole group. These values were lower for colorectal cancer (37 and 21 per cent 3 years after the second hepatectomy). These figures do not, however, convey the complete picture of the outcome for these patients. During the same follow-up period, 143 recurrences were detected and a mean of 2·9 resections per patient were performed. The indications for repeat hepatectomy are still to be clarified, although the surgical technique is safe.*

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The resection of hepatic metastases of colorectal origin, when possible, is still the only treatment that enables a 5-year survival rate of 33 per cent[1–3]. The resection of hepatic metastases of origin other than colorectal or hepatocellular carcinoma (HCC) gives similar results[4,5]. After hepatectomy, 40–60 per cent of patients will have recurrence only in the liver, whether the primary tumour is in the colorectum[6,7] or elsewhere[8,9]. Until now, there have been seven reported series of at least ten cases of repeat hepatectomy for tumour resection of malignant recurrence in the liver[10–16], of which the largest comprised 34 repeat hepatectomies carried out on 28 patients[10]. Although the published results are good, little is reported on the feasibility of repeat hepatectomy and the long-term outcome. To evaluate feasibility and survival, a prospective study was conducted on 41 patients who underwent 46 repeat hepatectomies in this institute.

Patients and methods

Between June 1984 and March 1992, 41 patients underwent repeat hepatectomy for recurrent malignant disease (five patients had a third hepatectomy). All but two patients had metastasis from colorectal, neuroendocrine or miscellaneous primary sites. Two patients underwent repeat hepatectomy for recurrent HCC. The 46 resections represented 16 per cent of 279 hepatectomies carried out for malignancy in this department during the study period. Sixteen patients had their first hepatectomy in another hospital. The 25 patients who had their first and second hepatectomies in this department represented 12 per cent of 217 patients who had a first hepatectomy for cancer in this institute. Ninety-five (44 per cent) of these patients had recurrence after a mean(s.d.) interval of 14(8) months; 65 per cent of recurrences were in the liver. A second liver resection was performed in 26 per cent of patients who had recurrence and in 40 per cent of those who had hepatic recurrence after the first liver resection. Selection criteria for repeat hepatectomy were: patient in good health, with recurrence only in the liver after a complete investigation, and recurrence that was technically resectable whatever the extent. The mean age of the 41 patients, 25 women and 16 men, was 54·7 (range 22–73) years. They were classified into groups 1–3 according to the site of the primary tumour (*Table 1*). One woman had malignancy of both colon and breast. Her first hepatectomy was for metastases of the colonic cancer and the second proved to be for metastases of the breast malignancy. Of the five patients who underwent a third hepatectomy, four were in group 1 and one in group 2.

The intervals between resection of the primary tumour and the hepatectomies are shown in *Table 1*. Synchronous resection of the primary lesion and metastases was carried out in 11 cases. One patient had 12 metastases of a carcinoid tumour that were completely resected in two successive hepatectomies. A 3-month interval was allowed for compensatory hypertrophy of the remaining liver parenchyma to occur between the two hepatic resections.

After primary liver resection, 12 patients in group 1 received

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systemic chemotherapy (5-fluorouracil (5-FU) and folinic acid) for 6 months. In group 2, three patients received systemic chemotherapy (5-FU and streptozotocin) for 6 or 8 months before primary hepatectomy; after this resection two received intra-arterial hepatic chemotherapy with the same drugs for 1 year. In group 3, all patients received systemic chemotherapy before and after the first hepatectomy and, in five cases, second-line chemotherapy after the second liver resection. The extent of hepatectomy at the first and second liver resections is shown in *Table 2*. Twenty patients had primary hepatectomies that were major (i.e. excision of at least three segments according to Couinaud's classification, or four metastases in the case of multiple wedge resections). Of these 20, eight underwent another major hepatectomy (i.e. excision of at least one-third of the remaining liver). Of the 21 minor hepatectomies at the first resection, nine were followed by major hepatectomy at the second procedure. Operations included one right hepatectomy extended to segment IV and one central hepatectomy; in three cases segment I was resected. For the four patients in group 1 the third liver resections were one right hepatectomy (after two consecutive wedge resections), excision of segment I (after removal of segment IV followed by a wedge resection), a segmentectomy IV (after a bisegmentectomy V–VI followed by a bisegmentectomy II–III) and a wedge resection (after a segmentectomy VIII followed by three wedge resections). The patient in group 2 underwent four wedge resections (after a bisegmentectomy II–III, followed by right hepatectomy).

Complete abdominal exploration was always undertaken before hepatectomy. Except in cases of primary liver malignancy, the previous midline laparotomy was extended by a right transverse incision after the exploration. On exploration in group 1 there were eight unsuspected extrahepatic recurrences. Intraoperative ultrasonography was performed routinely during all hepatectomies. Hepatic resection was usually carried out under intermittent pedicle clamping[17]. Continuous clamping[18] was used when total vascular exclusion of the liver was necessary (in five cases at first and in two at second hepatectomy). The

Table 1 *Site of primary tumour and interval between resection of the primary and the first, second and third hepatectomies*

	Colorectal (group 1; $n = 28$)	Neuroendocrine (group 2; $n = 5$)	Miscellaneous (group 3: $n = 8$)
Site of primary tumour	Colon 22 Rectum 6	Small bowel 3 Pancreas 1 Bronchial 1	Liver (hepatocellular carcinoma) 2 Breast 2 Stomach 1 Testis 1 Nephroblastoma 1 Small bowel sarcoma 1
Interval between resection of primary and first hepatectomy ($n = 41$) (months)*	11·6 (0–62)	146·0 (0–720)	28·4 (0–60)
Interval between first and second hepatectomy ($n = 41$) (months)*	17·3 (6–50)	28·8 (3–64)	18·6 (5–28)
Interval between second and third hepatectomy ($n = 5$) (months)	7, 15, 15, 18	84	—

*Values are mean (range)

Table 2 *Operative and postoperative features of first and repeat hepatectomies*

	Hepatectomy		
	First	Second	Third
No. of patients	41	41	5
Extent of resection*			
5 segments	1	1	0
4 segments	4	7	1
3 segments	12	4	1
1–2 segments	9	15	2
1 metastasectomy	6	6	0
>1 metastasectomy	9	8	1
Duration of operation (min)			
Mean(s.d.)	275(54)	275(68)	307(56)
Median (range)	270 (210–390)	277 (150–450)	285 (240–380)
Difficulty of liver exposure (%)			
Low	58	8	0
Moderate	13	24	20
Difficult	23	35	0
Very difficult	6	32	80
Duration of hepatic pedicle clamping (min)			
Mean(s.d.)	36(37)	54(27)	56(28)
Median (range)	22 (0–140)	60 (0–148)	53 (30–100)
Blood loss (ml)			
Mean(s.d.)	1690(1530)	1800(2115)	1710(1088)
Median (range)	1650 (500–7000)	1400 (0–12000)	1325 (1000–1700)
Mortality	0	1	0
Morbidity			
Local	4†	6‡	0
Systemic	10	7	1
Surgical reoperation	2	5	0

*According to Couinaud's classification. †Two haemorrhage and two subphrenic abscess; ‡five haemorrhage and one subphrenic abscess approach to the portal pedicles was mainly transparenchymal; early dissection of the porta hepatis was necessary only for centrohepatic tumours and for left hepatectomy extended to segments V and VIII[19].

The difficulty of surgery was estimated by the length of operation, duration of hepatic pedicle clamping, blood loss, consistency of the non-malignant hepatic parenchyma and difficulty of the liver exposure. The difficulty of exposure was classified into four levels: low (no abnormal adhesions), moderate (normal postoperative adhesions), difficult (the exposure took more than 2 h or there was blood loss above 1 litre), and very difficult (necessity to pass under the liver capsule or through the diaphragm). In two cases in group 1 preoperative hypertrophy of the potential remaining left lobe was induced by complete embolization of the right portal branch 4 weeks before resection, once before primary hepatectomy and once before secondary liver resection[20,21].

In ten cases in group 1 resection of extrahepatic tumour was performed at the same time as repeat hepatectomy (colon, two; abdominal wall, two; mesocolic lymph nodes, two; adrenal gland, two; ovary, one; small bowel, one). Each resected specimen was cut into 1-cm slices including tumour and liver parenchyma, fixed in Bouin's fluid, embedded in paraffin and cut to 4 μm in thickness. The routine stains included haematoxylin–eosin–saffron, chromotrope aniline blue for fibrous tissue, Turnbull's stain for iron and silver impregnation for reticulin fibres.

The data were collected prospectively. Survival curves were calculated according to the Kaplan–Meier method; no patients were lost to follow-up.

Results

Operation

The main difficulties encountered in repeat hepatectomy were re-exposure of the liver and dissection of the porta hepatis and inferior vena cava, especially if they had been dissected before. The approach to the liver was difficult or very difficult in 67 per cent of cases at the second liver resection and in 80 per cent at the third, while it was difficult in 29 per cent of primary hepatectomies (*Table 2*). For primary liver resection these difficulties occurred mainly if a previous surgical procedure had been carried out on the liver, gallbladder or hepatic artery. It was necessary to pass under the hepatic capsule to free the liver in six cases and the pleura was breached in five. In four cases it took 4 h to expose the whole liver and its vascular structures.

The mean duration of hepatic resection, as reflected by the clamping time of the pedicle, was 54 min for secondary hepatectomy and 36 min for primary resection (*Table 2*). As there was little difference between the extent of hepatic resection at the first and second operations, this suggests that the second resections were more difficult to perform than the first. It is interesting to note that in two cases the intermittent clamping time was more than 140 min without producing postoperative liver cell failure[17].

The median operative blood loss was 1·4 litres (*Table 2*), including resection of extrahepatic recurrence performed at the same time as hepatectomy. Resection of extrahepatic recurrence

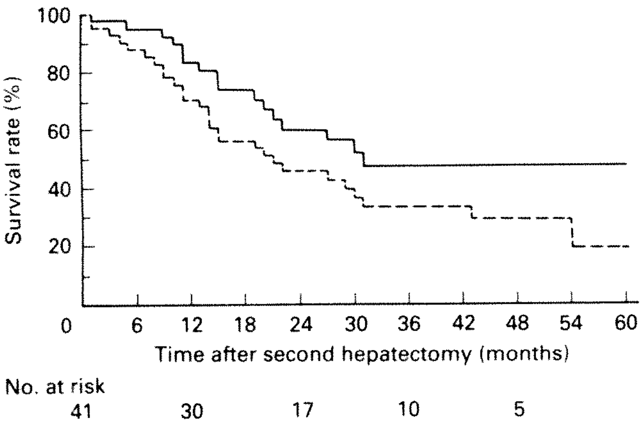

Figure 1 *Overall (——) and recurrence-free (– – –) survival from the time of second hepatectomy for 41 patients*

Table 3 *Pathological characteristics of tumours*

	Hepatectomy		
	First (*n* = 41)	Second (*n* = 41)	Third (*n* = 5)
Maximum diameter (cm)			
Mean(s.d.)	4·3(3·2)	3·8(2·2)	2·8(0·5)
Median (range)	4 (1–13)	4 (1–10)	3 (2–3)
No. of tumours			
Mean(s.d.)	1·7(1·4)	2·0(1·6)	2·2(1·3)
Median (range)	1 (1–7)	1 (1–8)	2 (1–4)
Minimum resection margin (mm)			
Mean(s.d.)	4·3(8·9)	5·1(8·7)	4·0(6·2)
Median (range)	3 (0–35)	2 (0–50)	2 (0–15)
Resection of extrahepatic recurrence	4	10	2
Positive pedicular nodes	1	2	1
Palliative resection*	5	5	0
State of non-tumour liver parenchyma (%)†			
Normal	81	20	0
Fibrosis or fatty infiltration	14	35	40
Fibrosis after chemotherapy	5	46	60

*Positive nodes of the hepatic pedicle, positive hepatic resection margin or unresected associated extrahepatic recurrence. †The histological state of the parenchyma was specified in 21 cases after first hepatectomy, in 26 after second and in all five cases after third resections

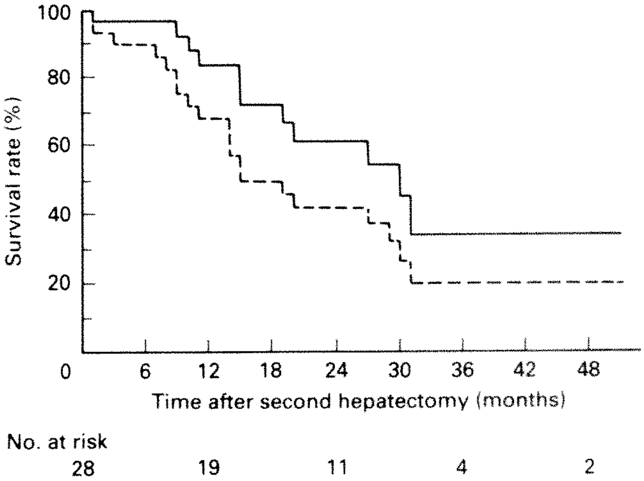

Figure 2 *Overall (——) and recurrence-free (– – –) survival from the time of second hepatectomy for 28 patients with colorectal carcinoma*

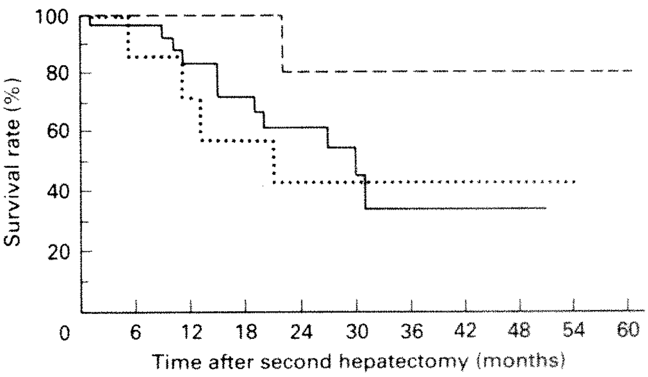

Figure 3 *Overall survival from the time of second hepatectomy for patients with primary tumours of colorectal (——; n = 28), neuro-endocrine (– – –; n = 5) or miscellaneous (·····; n = 8) origin*

Table 4 *Clinical status after repeat hepatectomy*

	Colorectal (group 1)	Neuroendocrine (group 2)	Miscellaneous (group 3)	Total
Dead				
No.	11	1	4	16
Median (range) interval after second hepatectomy (months)	15 (1–31)	22	12 (5–21)	16
Alive with recurrence				
No.	8	3	1	12
Median (range) interval after second hepatectomy (months)	29 (14–51)	50 (47–91)	40	40
Alive without recurrence				
No.	9	1	3	13
Median (range) interval after second hepatectomy (months)	10 (1–30)	83	43 (4–54)	22

Table 5 *Analysis of all 143 recurrences that developed in 41 patients who underwent repeat hepatectomy*

	Recurrence				
	First	Second	Third	Fourth	Fifth
No.	41	41	32	22	7
Interval between treatment of primary tumour and recurrence (months)*	12 (2–68)	27 (11–90)	40 (15–107)	58 (30–100)	60
Tumour recurrence					
Hepatic	34	32	19	13	4
Hepatic and lung	1	1	1	0	0
Hepatic and locally	6	2	2	0	0
Hepatic and other	0	1	3	1	0
Hepatic, lung and other	0	0	1	1	0
Lung	0	0	3	3	1
Locally	0	3	1	2	1
Other	0	2	2	2	1
Treatment					
Surgery	20	16	12	7	0
Surgery and radiotherapy	3	6	4	1	0
Surgery and chemotherapy	18	17	8	4	1
Radiotherapy	0	0	2	1	0
Chemotherapy	0	2	5	8	3
Radiotherapy and chemotherapy	0	0	1	1	1
Conservative	0	0	0	0	2

*Values are median (range)

Table 6 *Repeat hepatectomy: literature review of all series including at least ten repeat liver resections*

Year	Reference	No. of patients	No. of resections	Primary tumour	Mortality rate (%)	Morbidity rate (%)	Median follow-up after second hepatectomy (months)	No. of patients without recurrence	Median survival after second hepatectomy (months)
1989	Lange *et al.*[10]	28	34	Colorectal cancer 9 HCC 11	0	15	19	7	—
1990	Rees *et al.*[11]	12	12	Colorectal cancer 12	8	—	17	7	21
1990	Stone *et al.*[12]	10	10	Colorectal cancer 10	0	30	21	3	—
1990	Huguet *et al.*[13]	19	21	Colorectal cancer 8 HCC 9	5	52	24	7	—
1991	Gouillat *et al.*[14]	9	10	Colorectal cancer 7	0	0	17	3	17
1991	Borgonovo *et al.*[15]	23	27	Colorectal cancer 10 HCC 7	4	—	—	—	—
1992	Bozzetti *et al.*[16]	11	11	Colorectal cancer 11	9	40	17	4	23
1992	Present series	41	46	Colorectal cancer 28 HCC 2 APUDoma 5	2	32	20	13	34·5

HCC, hepatocellular carcinoma

(only in group 1) was twice as frequent at the secondary (24 per cent) as at the primary (10 per cent) hepatectomy.

Mortality and morbidity

Only one postoperative death (2 per cent) occurred before discharge from hospital, caused by acute bilateral nosocomial pneumonia that started during operation and did not respond to aggressive postoperative treatment. Although general complications (including pulmonary, urinary tract and abdominal wall infection, and pleural effusion) were no more numerous following primary than secondary liver resection (*Table 2*), local complications, especially haemorrhage, were more frequent after repeat hepatectomy and necessitated surgical intervention five times after the second liver resection but only twice after primary procedures. Complications were significantly more frequent when blood loss was greater than 1500 ml (70 per cent *versus* 16 per cent for loss under 1500 ml, $P=0{\cdot}04$).

Pathological characteristics

In 52 of the 87 hepatectomies (41 first, 41 second, five third), non-tumour liver tissue was examined histologically (*Table 3*). A relative increase in the extent of pathological liver tissue, especially fibrosis following chemotherapy, was observed at repeat hepatectomy. There was no significant difference between primary and secondary liver resection in the maximum tumour dimension, the number of tumours resected (a maximum of seven lesions in the first and eight in the second resection) and the mean minimum resection margin.

Outcome

Table 4 shows the current clinical status of the patients. Overall and disease-free survival after the second liver resection are shown in *Figure 1*. The 1-, 2- and 3-year overall survival rates after second hepatectomy were 84, 60 and 47 per cent, while 71, 46 and 33 per cent of patients were disease-free after the same intervals. Of the 28 patients who underwent secondary hepatectomy for colorectal metastasis, 21 per cent were alive and disease-free 3 years after the second liver resection (*Figure 2*). The prognosis of patients with tumours of neuroendocrine origin was significantly better than that of those with other primaries (*Figure 3*). Unfortunately, repeat hepatectomy was not the only treatment required by these selected patients during the course of the disease. The 41 patients developed 143 different recurrences (*Table 5*) during this period of limited survival (i.e. a mean of 3·5 recurrences per patient). A third recurrence occurred in 32 and a fourth in 22; seven patients developed a fifth recurrence at different sites. Two-thirds of the patients received complementary chemotherapy and/or radiotherapy.

Discussion

This series of patients who underwent repeat hepatectomy, which is believed to be the largest reported to date, indicates that this procedure is more difficult than primary liver resection but that it may be achieved with low morbidity and mortality; the role of repeat hepatectomy in the management of patients with recurrent metastatic malignancy after hepatic resection remains controversial.

Repeat hepatectomy is more difficult than primary resection for three reasons. First, re-exposure of the liver is difficult, especially where the previously resected edge adheres intimately to nearby organs. This is particularly likely after right hepatectomy or bisegmentectomy VI–VII, where the liver has turned through 90° and the resected edge adheres to the diaphragm. It is not unusual for the dissection to be subcapsular or inside the diaphragmatic muscle to allow mobilization of the liver. The same problem occurs when the hepatic pedicle and the inferior vena cava have been explored previously. In the present series this re-exposure was difficult or very difficult in 67 per cent of second and 80 per cent of third liver resections (*Table 2*).

Second, the liver parenchyma is more friable, and so more difficult to deal with, after hepatic regeneration and/or intensive chemotherapy (*Table 3*). After a relatively extensive first hepatectomy and compensatory hypertrophy, the liver parenchyma undergoes fatty infiltration[22] and so is more friable than in the normal state. This friability is also found in conditions of fibrosis following chemotherapy[23], and complicates haemostasis and biliostasis of the resected edge.

Third, after hepatic regeneration (especially when extensive) the vasculobiliary intraparenchymal anatomy is completely altered. This change is infinitely variable and depends both on the type of previous hepatectomy and on individual variations. Thus, leaving a margin of 5–10 mm of liver parenchyma along the right border of the median hepatic vein at right hepatectomy results, after regeneration, in a new right hepatic lobe, 3–4 cm thick, in which atypical vasculobiliary elements develop or hypertrophy. After extended right hepatectomy to segment IV, the anatomy of the remaining hypertrophied left liver is also modified, especially its three-dimensional orientation, and classical anatomical landmarks on the liver surface disappear. This 'neoanatomy' is not troublesome if carefully studied by intraoperative ultrasonography, which we believe to be essential if repeat hepatectomy is to be undertaken with safety.

Such operative difficulties explain the long time taken to perform these procedures (4–5 h) and the amount of blood lost (1·5–2 litres) in this series (*Table 2*).

This study and earlier reports in the literature (*Table 6*) all show low mortality and morbidity rates after repeat hepatectomy similar to those observed after primary liver resection. However, in both the cohort of Borgonovo *et al.*[15] and the present series the risk of bleeding seems higher than at primary resection. On the other hand, the risk of hepatic failure does not seem to be modified, mainly because the liver returns nearly to its original volume after primary resection. The indications for repeat hepatectomy should be the same as for primary resection with respect to patient characteristics (general condition, age, liver function) and tumour parameters (number, size, site, predicted resection margin). The same operative techniques can be used. From the technical point of view, repeat hepatectomy has been shown to be feasible and safe.

It is still difficult to state with confidence that survival times are improving. Until now, no large series of repeat hepatectomy has been published. Only three series[10,13,15] have included more than 15 patients and only two of these[10,13] give survival results, with respectively 25 and 36 per cent of patients disease-free and alive a mean of 20 months after the second liver resection. In the present series of 41 patients an overall survival rate of 48 per cent and disease-free survival rate of 33 per cent were observed 3 years after secondary hepatectomy. However, follow-up is limited and the number of long-term survivors small. Only eight patients survived more than 3 years, of whom two had recurrence at 42 and 54 months (*Figure 1*).

These results are encouraging and for the moment this therapeutic approach seems justified, but this optimism should be tempered by the frequency of recurrence at various sites (*Table 5*). Although this is a selected population by virtue of being suitable for liver resection, five patients had recurrence outside the liver and were treated curatively before presenting again with one or more liver metastases, ten patients had extrahepatic recurrence at the time of second hepatectomy and 32 had recurrence later. Twenty-two of these last patients were brought once again into complete remission. The 41 patients underwent a mean of 3 operations after resection of the primary tumour and two-thirds of them received chemotherapy and/or radiotherapy. There was an increase in the incidence of extrahepatic lesions after repeat hepatectomy: 10 per cent at the first, 24 per cent at the second hepatectomy and 40 per cent at the third operation. Although survival may be encouraging, it is at the cost of major and repeated interventions. It cannot yet be seen whether these patients can be cured in the long term, as no plateau appears on the survival curves. The same observation has been made with repeated treatment of local recurrence of colorectal cancer[24]. Only a longer period of follow-up with larger numbers can answer this question.

Analysis of the 28 patients who underwent second liver resection for a colorectal primary (*Figure 2*) is less encouraging, even with three patients exceeding 3 years' disease-free survival after this resection: only one of five patients is free from recurrence at 36 months. The selection criteria for repeat hepatectomy were the technical feasibility of performing complete resection of liver tumours and the exclusion of patients who had early and/or non-isolated liver recurrence. It seems that more restricted selection criteria may be appropriate. In metastases from neuroendocrine tumours, survival after the second liver resection is obviously superior to that observed for other primaries (*Figure 3*) as only one of the five patients died and the mean survival time is high (*Table 4*). This justifies a surgical approach of doing everything possible for patients with these tumours[25] even when complete long-term cure is not expected[26].

Are there any other curative procedures available for this population of selected patients with isolated hepatic recurrence after primary liver resection? Percutaneous ethanol injection gives good results when it is technically possible (small-sized tumours, not more than three in number and suitably placed)[27]. This technique is useful for patients in poor general condition. Liver transplantation has as yet no place in the treatment of hepatic metastases except perhaps for those of neuroendocrine origin, for which it is currently being evaluated. The role of transplantation for recurrence of HCC in the cirrhotic liver is also currently under evaluation.

A third hepatectomy is possible in very few selected cases, bearing in mind that it is a far more difficult procedure than a second resection. It is not yet possible to evaluate its benefit for survival.

In conclusion, it is clear that the technical problems of repeat hepatectomy have been solved as proven by the low operative mortality rate of this series. However, the length of remission that can be achieved by these extensive surgical procedures is not yet known. The indications for and results of repeat hepatectomy are independent variables that are still to be defined. This is difficult, as indications for the first hepatectomy for liver metastases are still not clear[3,28].

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Haemostasis after partial hepatectomy using argon beam coagulation

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The argon beam coagulator is a new device for haemostasis during and after surgery on parenchymatous organs. No data are available on its efficacy and tissue effect following hepatic resection. Blood loss, the time needed to achieve adequate haemostasis and histological findings after liver resection were assessed in 12 pigs using argon beam coagulation or suture ligation only, the mattress suture technique and tissue glue application. The treatment was randomly assigned to each of the four liver lobes in each pig. Median blood loss following argon beam coagulation was 13 (range 2–47) ml and after simple suture ligation 55 (range 2–260) ml ($P < 0{\cdot}02$)*. The median time needed for adequate haemostasis following argon beam coagulation was 3 (range 2–7) min* versus *14 (range 2–48) min in the control group* ($P < 0{\cdot}005$)*. There was no difference between argon beam coagulation and tissue glue, which were both superior to the use of mattress sutures. Argon beam coagulation resulted in less tissue damage than tissue glue or mattress suturing. The argon beam coagulator is an efficient device for achieving haemostasis following partial hepatectomy in the pig. It causes only a moderate tissue reaction.*

Since the beginning of liver surgery, surgeons have tried to control haemorrhage during operation on this highly vascularized organ. One of the problems encountered during liver surgery is the continuous oozing of blood from vessels that are too small to be ligated individually. Several techniques for controlling this kind of haemorrhage are currently available. A recent development is the use of argon beam coagulation. This is performed using a monopolar coagulator, which conducts radiofrequency current to the tissue using a jet of inert and non-flammable argon gas. The motion of current through the gas beam ionizes the argon, giving it a blue colour. It is the arcing of current into tissue, rather than any action of the argon gas, that leads to coagulation[1].

Although some reports have been published on argon beam coagulation in gynaecological[1], head and neck[2] and urological[3] surgery, few data are available on this haemostatic technique in procedures on the liver.

This study was designed to compare the efficacy of argon beam coagulation with that of three standard techniques in partial hepatectomy.

Materials and methods

Twelve pigs of Yorkshire–Danish Landrace crossbreed and bodyweight 22–30 kg were used. Part of each of the four lobes of the liver (left lateral, left medial, right medial and right lateral lobes) was resected using the blunt dissection method[4]. Because porcine liver lobes differ in size, care was taken to create resection surfaces of equal area. This was achieved by encircling the lobe with a 15-cm long tape to delineate the line of resection. Major vessels were ligated and other bleeding points sutured. The relative weights of each resected part of liver lobe in the 12 pigs, expressed as the mean(s.e.m.) proportion of total liver weight were: left lateral lobe 2·2(0·2) per cent; left medial lobe 3·5(0·3) per cent; right medial lobe 1·3(0·1) per cent; and right lateral lobe 2·4(0·2) per cent. The total amount of liver tissue resected in the 12 pigs, expressed as the mean(s.e.m.) proportion of total liver weight, was 9·4(0·4) per cent. The order in which the different lobes were operated on was randomly established.

After resection, the lobe was randomly assigned to one of four coagulation treatments: (1) control group ($n = 12$) in which no additional measures were taken; (2) suture group ($n = 12$) where 3/0 polydioxanone (PDS; Ethicon, Norderstedt, Germany) mattress sutures were inserted 0·5 cm from the resection edge, compressing the resected surface[5]; (3) tissue glue group ($n = 12$) in which Tissucol (Immuno, Vienna, Austria) was applied by jet spray in several layers[6], using a total of 1·0 ml per lobe; and (4) argon beam group ($n = 12$) in which an argon beam coagulator (Beamer One; Beacon Laboratories, Broomfield, Colorado, USA) was applied to the cut surface, 'painting' the whole area, at a setting of spray 1, level 3.

Before operation penicillin 600 000 units and streptomycin 600 mg were administered intramuscularly. All animals received 500 ml 35 per cent polydextran (Haemaccel; Behringwerke, Marburg, Germany) and 500 ml 0·9 per cent saline solution during operation to compensate for any blood loss.

Blood loss was estimated by weighing the swabs placed around each lobe after applying the coagulation treatment to the resected surface. Some 10 min after each technique was applied, the remaining bleeding points were sutured or coagulated with the conventional electrocoagulator. The time needed to achieve adequate haemostasis following coagulation was recorded. One pig was killed 3 h after operation and biopsy specimens of the freshly coagulated liver lobes

Table 1 *Blood loss and time to achieve adequate haemostasis with each coagulation technique in 12 areas of liver resection*

	Argon	Tissue glue	Mattress sutures	Control
Median (range) blood loss (ml)*	13 (2–47)	17 (1–62)	65 (7–860)	55 (2–260)
Median (range) time (min)†	3 (2–7)	5 (2–12)	9 (3–55)	14 (2–48)
No. of additional sutures	1	2	4	9
No. of additional coagulations	0	0	14	6
Mean no. of additional sutures and coagulations	0·1	0·2	1·5	1·2

*$P < 0{\cdot}02$ (argon *versus* control); $P < 0{\cdot}005$ (argon *versus* mattress sutures); $P < 0{\cdot}02$ (tissue glue *versus* control); $P < 0{\cdot}01$ (tissue glue *versus* mattress sutures). †$P < 0{\cdot}005$ (argon *versus* control); $P < 0{\cdot}001$ (argon *versus* mattress sutures); $P < 0{\cdot}01$ (tissue glue *versus* control); $P < 0{\cdot}01$ (tissue glue *versus* mattress sutures) (all Kruskal–Wallis test)

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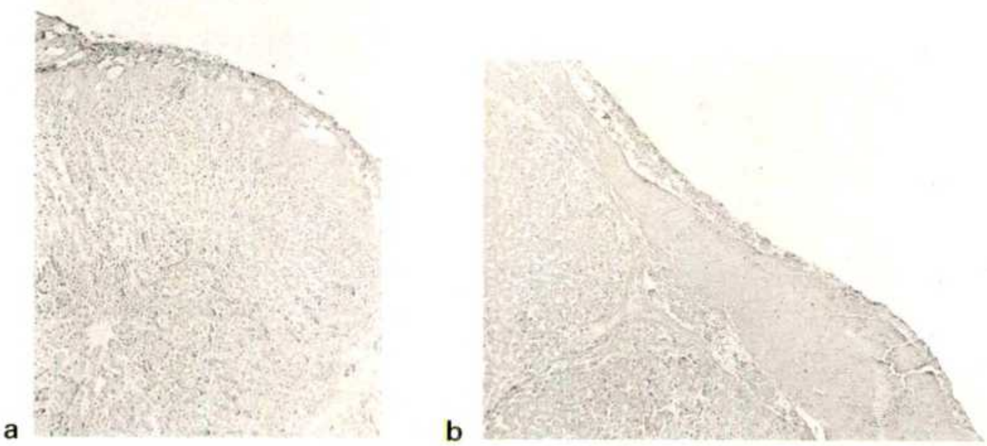

Figure 1 *Light microscopy of the liver lobes 3 h after operation.* **a** *Argon beam coagulation;* **b** *mattress suture technique. (Haematoxylin, azophloxin and saffron staining; original magnification ×40)*

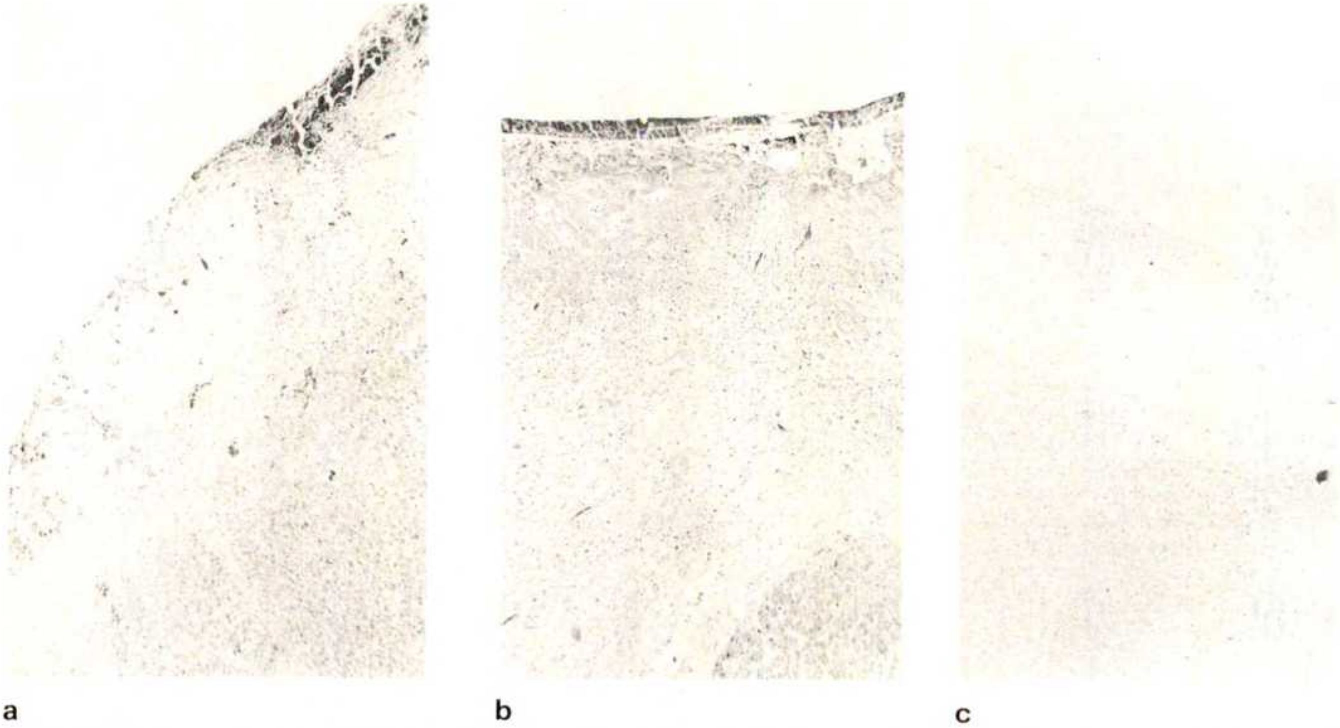

Figure 2 *Light microscopy of the liver lobes 1 week after operation.* **a** *Argon beam coagulation;* **b** *tissue glue technique;* **c** *control. (Haematoxylin, azophloxin and saffron staining; original magnification ×40)*

taken. The other pigs were killed 1 week after operation and specimens of the resected area taken. The specimens were fixed in formalin, sectioned and stained with haematoxylin, azophloxin and saffron for light microscopy. A Videoplan-assisted microscope (Kontron, Munich, Germany) was used to assess the depth of scar formation and fibrosis.

Results are given as median (range). Statistical analysis was carried out using the Kruskal–Wallis test. Statistical significance was assumed at $P < 0.05$. The study was approved by the Animal Experiments Committee of Erasmus University Rotterdam.

Results

There were significant differences between the techniques tested for blood loss, time to achieve haemostasis and depth of fibrosis on histological examination (Kruskal–Wallis test).

Blood loss

The blood loss in the 12 pigs with each coagulation technique is shown in *Table 1*. The smallest loss was seen with argon beam coagulation, the largest with mattress suturing. There was no difference in blood loss between the argon beam and tissue glue techniques, or between mattress suture and control methods. However, blood loss with argon beam and tissue glue haemostasis was considerably less than that with the mattress suture and control techniques. When all four methods were considered together, there were no differences in blood loss between the different liver lobes and the amount of loss was not linked to the order of resection (first, second, third or fourth lobe).

Time to achieve adequate haemostasis

With argon beam coagulation, haemostasis was quickly achieved, while the control technique took the longest (*Table 1*). There was no significant difference between argon beam coagulation and the tissue glue technique. Again, both the argon beam and tissue glue methods were superior to the other two.

Table 2 *Depth of fibrosis 1 week after operation*

	Median (range) depth of fibrosis (mm)
Argon	1·7 (1·2–4·5)
Tissue glue	2·6 (1·2–2·9)*
Mattress sutures	2·2 (1·0–5·3)
Control	1·5 (1·1–3·7)

*$P < 0{\cdot}01$ (tissue glue *versus* control, Kruskal–Wallis test)

Number of additional sutures and coagulations

The smallest number of additional sutures and conventional electrocoagulations was needed following partial lobectomy using argon beam haemostasis (*Table 1*). The largest number of additional sutures was required following the control technique. The largest number of additional electrocoagulations was needed after mattress suturing. The largest number of additional sutures plus additional electrocoagulations had to be used following the mattress suture technique.

Autopsy findings

Autopsy 1 week after resection showed a large number of adhesions between the resected liver lobes and surrounding organs. There was no correlation between the technique used and the number or severity of adhesions. Nearly all pigs had some ascites in the abdomen; this was not haemorrhagic.

Histology

Histological examination of the liver lobes 3 h after operation showed that following argon beam coagulation there was a thin layer (about one lobule in thickness) of coagulation necrosis (*Figure 1*). The lobe treated with tissue glue demonstrated a layer of fibrin on top of largely viable liver parenchyma, with a small area of regressive and haemorrhagic abnormalities. In the lobe treated with mattress sutures, a layer with ischaemia and necrosis of moderate thickness was seen (*Figure 1*). The lobe treated using the control technique showed some necrosis, sharply confined to a very thin layer of tissue. There were no abnormalities in the remainder of the liver parenchyma after coagulation with the different techniques.

By 1 week after resection and coagulation, the lobes treated using argon beam coagulation showed, from the top downward, a small layer with fibrin deposition, a broad layer of necrotic parenchyma containing many neutrophil granulocytes, and a layer showing an acute inflammatory reaction with active fibroplasia. In the lobes treated with tissue glue, a very active proliferative inflammatory reaction with coagulation necrosis in some areas and a foreign body reaction in others could be seen around the necrotic parenchyma (*Figure 2*). The lobes treated with mattress sutures demonstrated a broad and irregular fringe of fibrosis and an active proliferative inflammatory reaction. There was a distinct foreign body reaction around the sutures. In the lobes treated using the control technique, a mild proliferative inflammatory reaction with a small fringe of fibrosis was noted (*Figure 2*). The remainder of the liver parenchyma demonstrated no abnormality following haemostasis with the different techniques.

The depth of fibrosis in the liver was significantly different between the groups ($P < 0{\cdot}01$, Kruskal–Wallis test). After tissue glue haemostasis, the median area of fibrosis was deeper (2·6 (range 1·2–2·9) mm) than that after the control technique (1·5 (range 1·1–3·7) mm) ($P < 0{\cdot}01$). The depth of fibrosis after the other techniques was between these two extremes (*Table 2*).

Discussion

These results demonstrate the superiority of argon beam coagulation and tissue glue over mattress suture and control techniques used for haemostasis following partial hepatectomy. This was the case both for the severity of blood loss and the time needed to achieve adequate haemostasis. The pig was chosen as an experimental animal because of similarities between porcine and human liver parenchyma. Because the pig has four liver lobes it was possible to use four different coagulation techniques in each animal.

Blood pressure was not measured during operation because previous investigators[4] have shown there to be no relationship between blood pressure and the amount of blood lost during partial hepatectomy in pigs. The present study has confirmed that there is no relationship between the individual porcine liver lobe and the amount of blood loss during resection[4]. There was no influence of the order of resection on the amount of blood loss per lobe.

As expected, the control technique gave the least disruption of liver parenchyma and the least fibrosis. Argon beam coagulation was second best in this respect. The mattress suture technique caused considerable ischaemia and thus necrosis. There was also an impressive foreign body reaction to the sutures.

Depth of fibrosis, after 1 week of healing, was used as a parameter for the loss of liver parenchyma. It was smallest with the control technique and largest with tissue glue. The fact that tissue glue produces the greatest fibrosis is probably due to the stimulating effect on fibroblast growth of fibrin and factor XIII, which form the major constituents of Tissucol once the components of the glue (fibrinogen, thrombin, factor XIII, calcium chloride and aprotinin) have reacted with each other[6]. This may therefore represent increased fibrosis on the liver surface, and may not necessarily reflect tissue destruction.

Argon beam coagulation has several advantages over conventional electrocoagulation. The depth and horizontal extent of coagulation are relatively fixed, which is not the case with the conventional procedure. The argon beam blows blood away from the tissue, thereby giving better cauterization and visualization[2]. Furthermore, the argon gas jet reduces the availability of oxygen at the desiccation site, resulting in less smoke[3]. Another difference is that the argon beam coagulator functions in a non-contact manner[2], thereby allowing the bleeding surface to be 'painted'.

In conclusion, the argon beam coagulator is a useful device and a promising addition to the surgical armamentarium for liver resection.

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Prolonged normothermic ischaemia of human cirrhotic liver during hepatectomy: a preliminary report

To evaluate the tolerance of the cirrhotic liver to extended warm ischaemia, 47 patients with cirrhosis who underwent liver resection over a 4-year period were studied retrospectively. Three groups of patients were identified. In group 1 (14 patients) liver resection was performed under conditions of portal triad occlusion ranging from 50 to 75 (mean 57·1) min. Group 2 (12 patients) was treated with portal occlusion for a period ranging from 30 to 42 (mean 33·1) min. Group 3 comprised 21 patients who underwent hepatectomy using conventional techniques. Mean blood loss was significantly reduced by portal triad occlusion (819 ml in group 1, 523 ml in group 2) compared with the conventional technique (1652 ml in group 3) ($P < 0.05$, group 1 versus *group 3;* $P < 0.01$, *group 2* versus *group 3). Hospital death occurred in three of the 21 patients in group 3 but in no patient who underwent portal triad occlusion. The morbidity rate was lower in the two occlusion groups (four of 26 patients) than in group 3 (six of 21). Bilirubin metabolism was substantially better after surgery in the occlusion groups* ($P < 0.05$, *groups 1 and 2* versus *group 3 at day 14). Although the serum levels of transaminases were significantly raised until day 3 in patients undergoing long-term occlusion, the cirrhotic liver withstood the ischaemia–reperfusion insult, as assessed by changes in hepatic microcirculation, lipid peroxidation and the morphology of hepatic sinusoids. It is concluded that prolonged ischaemia during liver resection can be sustained in patients with cirrhosis and without high-risk factors.*

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The liver can withstand inflow occlusion[1–3] for up to 1 h. It remains to be clarified whether this applies when the hepatic parenchyma is abnormal. Other workers have found that the cirrhotic liver tolerates warm ischaemia for longer than the 'accepted' limit[4,5] of 15–20 min. Reduction of blood loss has resulted in fewer complications after hepatic resection[2,6,7] and the present authors introduced this practice from August 1987. Massive bleeding during hepatectomy often results in serious consequences, particularly in patients with cirrhosis who have metabolic and coagulation disorders, and a hyperdynamic circulation[8,9].

The clinical course of 26 patients with liver cirrhosis in whom normothermic ischaemia of >30 min duration had been induced was evaluated retrospectively. These patients were compared with those with cirrhosis who had undergone partial liver resection using conventional techniques.

Patients and methods

Between August 1987 and July 1990, 26 patients with cirrhosis underwent liver resection (segmental or subsegmental) with prolonged occlusion of the portal triad. To effect the occlusion, a tape was placed around the portal triad. Parenchymal transection was facilitated with an ultrasonic dissector (CUSA; Cavitron, Stanford, Connecticut, USA). A local haemostatic agent (microfibrillar collagen Hemo-stat; Alcon, Humacao, Puerto Rico) was applied to the raw surface of the transected liver to control oozing. Anaesthesia was maintained by use of enflurane supplemented with nitrous oxide. A cephalosporin (1·0 g cefotiam or cephazolin) was administered intravenously to all patients during resection. The mean(s.d.) central venous pressure during occlusion was 8·0(2·5) cmH_2O.

The 26 patients were divided into two groups according to the period of occlusion. Patients in group 1 ($n = 14$) underwent long-term inflow occlusion ranging from 50 to 75 min. In group 2 ($n = 12$) portal triad occlusion of medium-term duration (30–42 min) was performed during hepatectomy. Group 3 consisted of 21 patients with cirrhosis in whom liver resection was carried out by conventional methods using manual parenchymal compression, liver clamping, temporary inflow occlusion for < 10 min or a combination of these. All but three patients in group 3 underwent surgery between September 1986 and May 1988.

Liver cirrhosis and carcinoma were diagnosed histologically in all 47 patients. There were 41 men and six women with a mean age of 60·2 (range 37–80) years. The estimated blood loss, coagulation profile, serum biochemistry, postoperative complications and mortality were compared. To evaluate ischaemia–reperfusion injury to the liver, tissue blood flow, lipid peroxidation and histology were studied during operation in the last 11 patients subjected to long-term ischaemia. Flow was measured using a laser Doppler flowmeter (BPM403; TSI, St Paul, Minnesota, USA)[10]. The Doppler probe was placed randomly on the liver until a stable flow value was obtained. The mean of at least three determinations was taken as the representative value. The degree of lipid peroxidation was estimated by measuring the stable end-product of the reaction, liver tissue malondialdehyde (MDA), by a colorimetric reaction with thiobarbituric acid as described by Ohkawa *et al.*[11].

All values are expressed as mean(s.d.), although standard error of the mean is shown in figures to reduce overlap. Statistical analysis was performed using analysis of variance by Scheffé's method and Student's t test or the χ^2 test (High-quality Analysis Libraries for Business and Academic Users; G. Sugakusha, Tokyo, Japan). $P < 0.05$ was considered significant.

Results

Patient profiles

Clinical details of the patients are shown in *Table 1*. There were no significant differences between the groups with respect to clinical data. No more than 50 min occlusion was allowed for patients with Child's grade C disease. The majority of patients underwent subsegmentectomy. Four patients in group 3

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Table 1 *Clinical profiles of patients with liver cirrhosis undergoing portal triad occlusion compared with controls*

	Long-term occlusion (group 1; $n = 14$)	Medium-term occlusion (group 2; $n = 12$)	Standard technique (group 3; $n = 21$)
Ischaemia time* (range) (min)	57·1(8·4) (50–75)	33·1(3·7) (30–42)	—
Age (years)*	56·8(6·5)	63·1(7·7)	60·8(8·9)
Sex ratio (M:F)	13:1	11:1	17:4
Child's grade			
A	8	4	15
B	6	6	5
C	0	2	1
Indocyanine green clearance test at 15 min (%)*	17·3(7·4)	22·9(8·2)	20·6(9·8)
Alanine aminotransferase (units/l)*	64(24)	64(24)	74(67)
Bilirubin (mg/dl)*	0·79(0·29)	1·03(0·43)	0·97(0·40)
Albumin (g/dl)*	3·7(0·5)	3·5(0·5)	3·6(0·4)
Prothrombin time (%)*	94·1(21·4)†	90·9(24·1)	80·0(14·1)
Weight of resected liver (g)*	115(127)	103(127)	116(85)

*Values are mean(s.d.); †$P < 0{\cdot}05$ (group 1 *versus* group 3, Student's *t* test)

Table 2 *Postoperative morbidity and mortality*

	Long-term occlusion (group 1; $n = 14$)	Standard technique (group 3; $n = 21$)
Abscess	2 (14)	2 (10)
Pleural effusion	2 (14)	5 (24)
Adult respiratory distress syndrome	0 (0)	3 (14)
Coagulopathy	1 (7)	4 (19)
Liver failure	0 (0)	3 (14)
Hospital death	0 (0)	3 (14)

Values in parentheses are percentages

underwent segmentectomy (right posterior segment, one patient; left lateral segment, three). There were five patients in groups 1 and 2 in whom hepatic segments or similar amounts of tissue had to be resected (right posterior segment, one patient; left lateral segment, three; resection of Couinaud segments V and VII, one). In two patients a second hepatectomy with portal triad occlusion was performed.

Blood loss and plasma replacement

The mean(s.d.) estimated blood loss during surgery was significantly lower ($P < 0{\cdot}05$ and $P < 0{\cdot}01$) in the occlusion groups (group 1, 819(572) ml; group 2, 523(457) ml) than in group 3 (1652(1240) ml). The mean(s.d.) plasma requirement up to day 7 after operation was 3351(1079) ml in group 1, 2433(1308) ml in group 2 and 4208(1792) ml in group 3. There were no intraoperative adverse effects of portal triad occlusion on systemic haemodynamics.

Postoperative morbidity and mortality

As shown in *Table 2* there were three hospital deaths in group 3, all a result of liver failure. Postoperative mortality was nil in the 26 patients treated by portal triad occlusion. Six patients in group 3 had one or more postoperative complications, including fatal ones. The three who died had a combination of liver failure, coagulopathy, adult respiratory distress syndrome and pleural effusion. In the other three patients subphrenic abscess occurred in two and massive pleural effusion in one. There was no morbidity in patients in group 2. In group 1 four patients had complications: pleural effusion, two; abscess, two; and coagulation disorder, one. The overall morbidity rate of patients treated with portal triad occlusion was 15 per cent.

Liver function tests and coagulation profiles

Serum transaminase levels reached a peak on day 1 after surgery in all groups (*Figure 1*). There were no significant differences between groups 2 and 3. However, in group 1 long-term occlusion induced a significant rise in transaminase activity compared with levels in groups 2 and 3. There were no significant differences in total bilirubin level between the groups up to day 7 after operation (*Figure 2*). Bilirubin levels in the

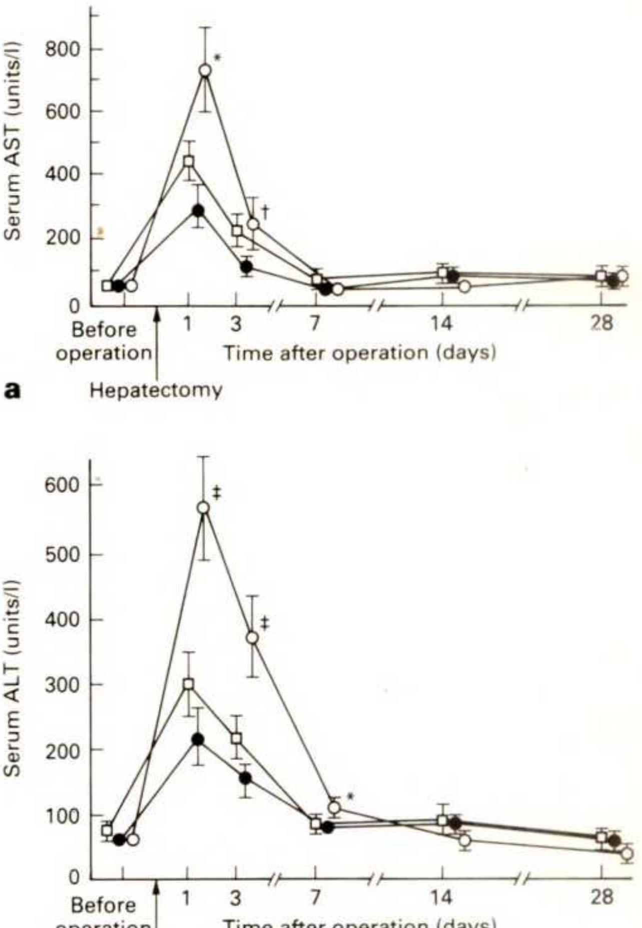

Figure 1 *Serum levels of* **a** *aspartate aminotransferase (AST) and* **b** *alanine aminotransferase (ALT) following liver resection with (groups 1 and 2) and without (group 3) portal triad occlusion. Values are mean(s.e.m.).* ○, *Group 1;* ●, *group 2;* □, *group 3.* *$P < 0{\cdot}02$, †$P < 0{\cdot}05$ *(group 1* versus *group 2);* ‡$P < 0{\cdot}02$ *(group 1* versus *groups 2 and 3) (Student's* t *test)*

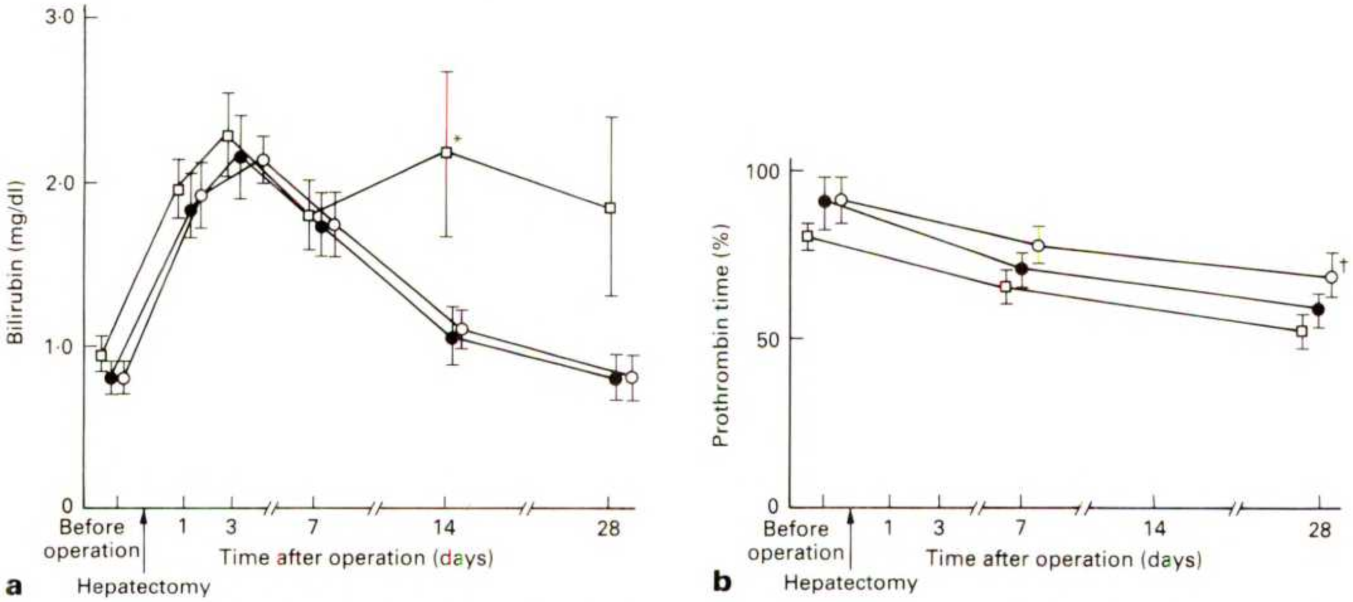

Figure 2 **a** *Serum levels of total bilirubin and* **b** *prothrombin time following liver resection with and without portal triad occlusion. Values are mean(s.e.m.); data on prothrombin time were not available from all patients.* ○, *Group 1;* ●, *group 2;* □, *group 3.* *P < *0·05* (*group 3* versus *groups 1 and 2*); †P < *0·05* (*group 1* versus *group 3*) (*Student's* t *test*)

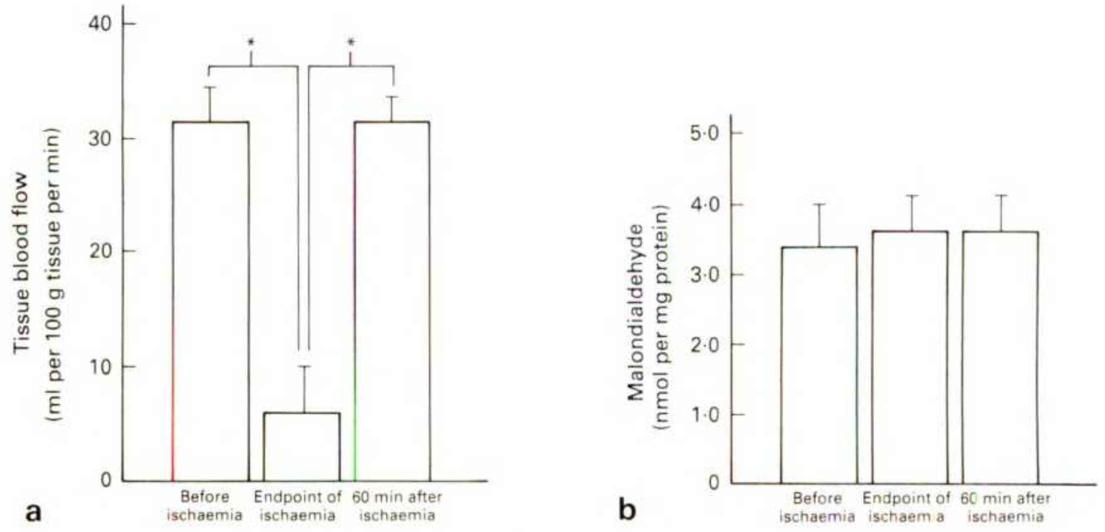

Figure 3 **a** *Tissue blood flow* (*ten patients*) *and* **b** *level of malondialdehyde* (*11 patients*) *in the cirrhotic liver during ischaemia–reperfusion following >50 min normothermic ischaemia. Values are mean*(*s.e.m.*). *P < *0·001* (*Student's* t *test*)

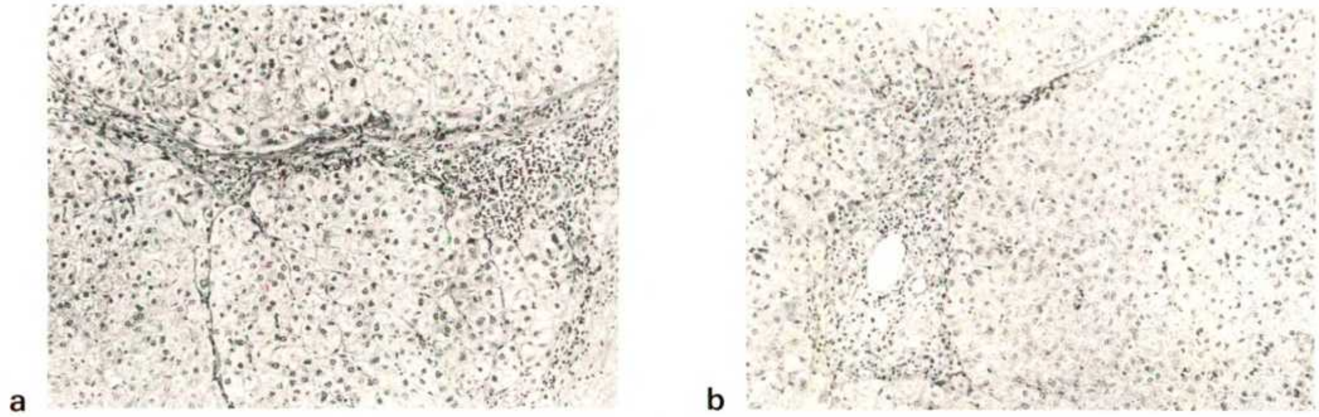

Figure 4 *Photomicrographs of cirrhotic liver* **a** *before and* **b** *1 h after 55 min portal triad occlusion. Hepatic architecture was well maintained.* (*Haematoxylin and eosin stain, original magnification* × *90*)

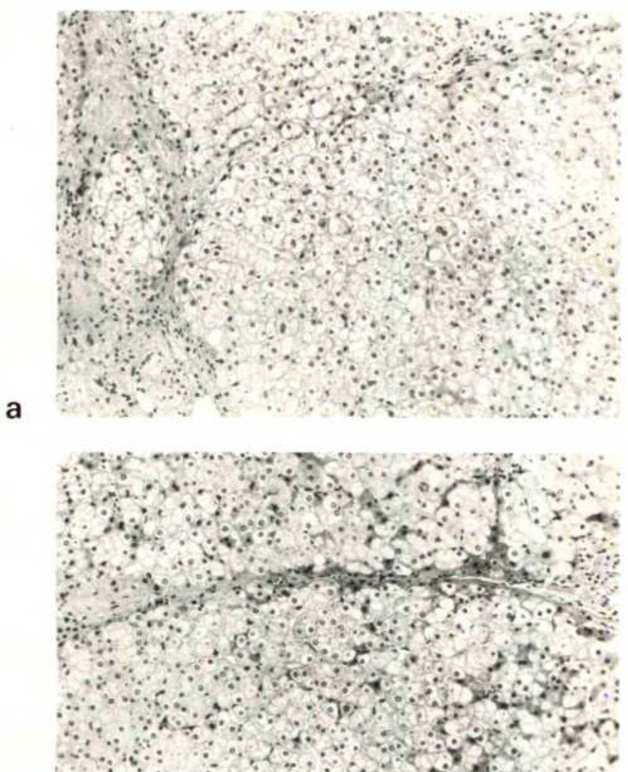

Figure 5 *Photomicrographs of cirrhotic liver* **a** *before and* **b** *1 h after 75 min portal triad occlusion.* **a** *Early stage of liver cirrhosis.* **b** *Note good preservation of hepatic sinusoids, despite degenerative changes (oedema and eosinophilia) in the hepatocytes. (Haematoxylin and eosin stain, original magnification × 90)*

control patients remained high thereafter, while values in the occlusion groups decreased. There was a significant difference between the three groups on day 14. Prothrombin time in group 1 remained higher than that in group 3 (*Figure 2*).

Liver tissue blood flow and determination of malondialdehyde concentration

Figure 3a shows liver tissue blood flow in group 3. The mean(s.d.) preclamping value of 32·0(10·6) ml per 100 g tissue per min fell during occlusion to 6·3(4·1) ml per 100 g per min. This finding confirmed the efficacy of the method used to occlude hepatic inflow. The flow recovered to preoperative levels 60 min after hepatic recirculation. There were no differences in MDA levels before, during or 60 min after warm ischaemia (*Figure 3b*).

Histology

As shown in *Figure 4* there was no evidence of ischaemia–reperfusion injury to the liver after 55 min of portal triad occlusion. Even after 75 min of hepatic inflow occlusion, the hepatic sinusoidal structure was well preserved in patients with early cirrhosis; however, eosinophilic changes in the hepatocytes were evident (*Figure 5*).

Discussion

Huguet *et al.*[1] reported that the human liver can tolerate warm ischaemia for > 60 min. This has been confirmed by other researchers[2,3]. Pigs and dogs can also tolerate hepatic inflow occlusion for longer than expected, if venous stagnation of the abdominal viscera is avoided by portosystemic shunting[12–14]. In the early 1900s, it was thought[15] that cirrhotic human livers could not withstand porta hepatis occlusion > 15 min, but this has recently been shown not to be the case. Nagasue *et al.*[4,5] found that the cirrhotic liver can tolerate up to 47 min of warm ischaemia, and Elias and colleagues[16] reported satisfactory tolerance of abnormal hepatic parenchyma to intermittent prolonged ischaemia lasting > 90 min. Yamaoka *et al.*[17] recently reported that cirrhotic human liver can tolerate 60 min of total vascular exclusion.

In the present study cirrhotic human liver withstood continuous occlusion for up to 75 min. There was no mortality and the overall morbidity rate was 15 per cent. Long-term portal occlusion (> 50 min) caused some parenchymal hepatocyte injury, with a substantial rise in serum transaminase activity, while medium-term ischaemia decreased serum enzyme levels compared with conventional procedures. Despite significant hepatocyte injury, the cirrhotic liver tolerated the ischaemia. There is evidence that in ischaemia–reperfusion injury liver integrity is affected mainly by the condition of non-parenchymal sinusoidal lining cells[18–20].

To evaluate damage to the cirrhotic liver, the production of tissue MDA, a biochemical marker of oxidative stress, was determined[11]. The MDA levels of liver subjected to long-term inflow clamping remained steady during ischaemia and for 60 min after reperfusion. This indicates that the lipid peroxidation reaction, mediated by oxygen radicals in the cirrhotic liver, was not clinically significant, although the technique employed may not be sufficiently accurate to detect minor changes unless high-performance liquid chromatography is used to measure thiobarbituric acid.

Histologically, satisfactory preservation of the hepatic endothelium during ischaemia–reperfusion was found, despite degenerative changes in hepatocytes. To evaluate further the integrity of the sinusoidal lining system, liver tissue blood flow was measured. Coincident with morphological and biochemical data, the hepatic microcirculation was well maintained following ischaemia. Thus, the cirrhotic liver can withstand continuous inflow occlusion if the sinusoidal lining system is intact. With regard to parenchymal hepatocyte injury, about 50 min is the limit beyond which hepatocytes are substantially damaged.

The present data show that flow in the liver tissue after portal triad occlusion was maintained at approximately 20 per cent of the level before ischaemia although the liver became pale immediately after tape occlusion. These observations can be explained by retrograde flow of blood from the vena cava into the hepatic veins. Active bleeding from the hepatic veins was sometimes encountered during parenchymal dissection under the control of hepatic inflow, as was found by Nagasue *et al.*[5]. We speculate that this back flow contributes to the maintenance of liver function.

Portal triad occlusion enables sufficient time to be gained to complete the resection, and to identify and ligate vascular and biliary structures in a bloodless field. Indeed, continuous occlusion in the present patients resulted in substantial reduction of intraoperative bleeding and less plasma had to be administered after surgery. The reduced blood loss was associated with fewer perioperative complications, in agreement with results from other studies[2,6,7]. The procedure is simpler than other techniques, such as selective control of hepatic inflow[21].

Because the cirrhotic liver is more vulnerable to ischaemia than the healthy organ, the possible risks of occlusion, particularly hepatic insufficiency, should be borne in mind. Although the advisability of the routine use of this procedure may be debatable, the present data show that some cirrhotic livers tolerate continuous warm ischaemia of about 50 min, a time sufficient to complete resection safely. The authors' working policy is that, under conditions of portal triad occlusion, local resection of a lesion located in the superior portion or deep within the central part of the liver is feasible if the cirrhotic changes are moderate, for instance in patients with Child's grade A or, perhaps, grade B disease. A patient with liver cirrhosis but with no high-risk factors can tolerate prolonged ischaemia during hepatectomy.

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Laparoscopic ultrasonography for hepatobiliary and pancreatic malignancy

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Despite the advances made since the introduction of ultrasonography, computed tomography and magnetic resonance imaging, a wide discrepancy may occur between preoperative and peroperative staging of gastrointestinal malignancy with liver and peritoneal metastases. Diagnostic laparoscopy performed immediately before a planned laparotomy can provide valuable information for the accurate assessment and appropriate management of some forms of gastrointestinal malignancy, especially that of the liver and pancreas. For evaluation of small liver and retroperitoneal malignancies, intraoperative ultrasonography performed by laparotomy is of proven value. It is now technically possible to perform ultrasonography through a laparoscopic cannula using high-resolution ultrasonographic transducers. This combination of laparoscopy and ultrasonography was studied in 25 patients with established liver lesions, carcinoma of the gallbladder or pancreatic cancer. Additional information leading to a change in surgical approach was obtained in 20 patients. Laparoscopic ultrasonography, although still in a preliminary phase of development, is a simple and reliable technique that will contribute to more accurate staging of intra-abdominal malignancy.

Imaging of abdominal organs, especially the liver and pancreas, has greatly improved with the introduction of ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI)[1,2]. Although these techniques afford considerable advantages, the surgeon dealing with gastrointestinal malignancy is often faced with a discrepancy between preoperative and peroperative staging, due mainly to the presence of liver and peritoneal metastases. In cancer of the oesophagus, gastric cardia, liver and pancreas, more accurate staging before operation is desirable because surgery may not be the best palliative treatment when metastases are present[3–5]. Laparoscopy performed immediately before a planned laparotomy will enable visualization of these metastases and prevent unnecessary operation.

Laparoscopy is limited in the assessment of less obvious hepatic and retroperitoneal malignancies, but ultrasonography performed during laparotomy has proven its value for these lesions. For hepatic tumours and liver metastases from colorectal cancer, this technique gives significant additional information, leading to a change in surgical approach in 30 per cent of patients[6,7]. The exact diagnosis of hepatic lesions, and knowledge of their number and precise localization, are essential when considering liver resection or adjuvant therapy.

It is now possible to perform laparoscopic ultrasonography of the liver and pancreas by introduction of an ultrasonographic transducer through a cannula[8]. This technique, combining inspection and ultrasonography, has been used in the preoperative assessment of 25 patients with established liver lesions, carcinoma of the gallbladder or pancreatic cancer. Preoperative assessment was by ultrasonography, CT and MRI. Special attention was paid to the additional information provided by laparoscopic ultrasonography, particularly when it led to a change in surgical approach.

Patients and methods

Between October 1990 and February 1992, 25 patients underwent laparoscopic ultrasonography immediately before a planned surgical intervention for hepatobiliary–pancreatic lesions. Ultrasonography, CT and MRI were used before operation. Hepatic lesions were found in 19 patients during the investigation of abdominal pain (two patients), breast cancer (three), colorectal cancer (two), primary liver cancer (three) and oesophageal cancer (one), and follow-up of colorectal cancer (six), ovarian cancer (one) and carcinoid syndrome (one). Five patients had potentially curable pancreatic cancer and another carcinoma of the gallbladder. In all 25 patients, a surgical procedure was indicated, but no certainty of resectability was offered by the preoperative investigation.

Selection criteria for laparoscopic ultrasonography

The selection criteria for laparoscopic ultrasonography were: (1) the presence of hepatic lesions with no certainty regarding diagnosis (i.e. lesions found during investigation for abdominal pain); (2) hepatic lesions found during staging of tumours other than gastrointestinal cancer (e.g. breast cancer) and where the correct diagnosis is decisive for further treatment; (3) the need to ascertain resectability of hepatic metastases (from colorectal cancer) when doubt existed before operation regarding the number of tumours; (4) evaluation of metastases in primary liver cancer and determination of its resectability in relationship to hepatic vascular structures; and (5) preoperative assessment of the operability of gallbladder and pancreatic cancer.

Criteria for resectability on laparoscopic ultrasonography

The criterion for resectability of patients with liver metastases from colorectal cancer was the presence of fewer than four metastases in the whole liver parenchyma.

For primary liver carcinoma, the only criterion was the possibility of performing radical resection, up to extended right or left hemihepatectomy. Extension of the cancer outside the liver indicated unsuitability for resection.

For gallbladder carcinoma, spread of the tumour outside the gallbladder and its hepatic bed, such as metastases in the liver, obstruction of the confluence of the bile duct and peritoneal metastases, implied irresectability.

For pancreatic cancer, the criteria for irresectability were: (1) the presence of liver or peritoneal metastases; (2) visualization of the tumour in the hepatoduodenal ligament or outside the duodenum (indicating that radical resection was not possible); (3) the presence of portal hypertension; and (4) encasement or thrombosis of the portal vein (seen on ultrasonography).

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Technique

Laparoscopic ultrasonography was performed under general anaesthesia. After the induction of pneumoperitoneum, the laparoscope was introduced in the lower aspect of the umbilicus or through the lateral aspect of the rectus muscle. A 5-mm cannula was introduced in the anterior axillary line under the costal margin to retract the liver. After inspection of the peritoneal cavity, the liver was examined for lesions on the superior and inferior surfaces of both lobes. A 20-mm sheath was introduced below the right costal margin in the mid-clavicular line (*Figure 1*), under direct vision to prevent injury. This wide cannula permitted introduction of a 16-mm linear-array cylindrical 5-MHz transducer (Aloka, Tokyo, Japan) (*Figure 2*). The transducer was placed under direct vision on the right superior surface of the liver, which was then examined in the same way as during laparotomy. In patients with pancreatic cancer, the probe was placed on the hepatoduodenal ligament and pancreatic area to localize the tumour and its relation to the portal vein and superior mesenteric artery.

Confirmation of the diagnosis by laparoscopic ultrasonography

First, lesions were identified by inspection and ultrasonography and, in all cases where inoperability was determined by laparoscopic ultrasonography, biopsies were taken to confirm the diagnosis, either with a biopsy forceps or a biopsy needle guided ultrasonographically.

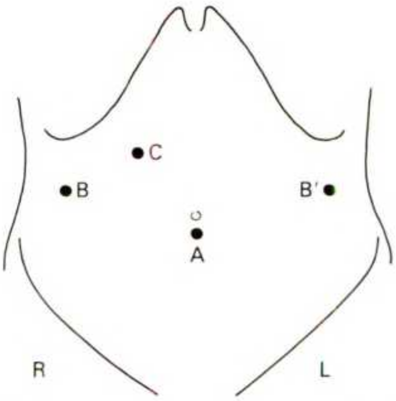

Figure 1 *Positions for cannula placement during laparoscopic ultrasonography. A, 10 mm (for laparoscope); B, 5 mm (for retraction and palpation); B', alternative site to B; C, 20 mm (for ultrasonographic transducer)*

Results

A total of 25 patients (eight men, 17 women) met the criteria for preoperative assessment by laparoscopic ultrasonography. Patient age ranged from 26 to 72 (mean 56) years. Diagnoses made by laparoscopic ultrasonography were compared with those made before operation (*Tables 1* and *2*).

In the evaluation of hepatic lesions found during investigation for abdominal pain, haemangiomas were found by laparoscopic ultrasonography in one patient and carcinoid metastases in the other.

Of the three patients with breast carcinoma, one had haemangiomas, another had several metastases, while the third had a paraganglioma of adrenal origin adjacent to the liver. In the two patients without metastases, laparoscopy was followed by mastectomy.

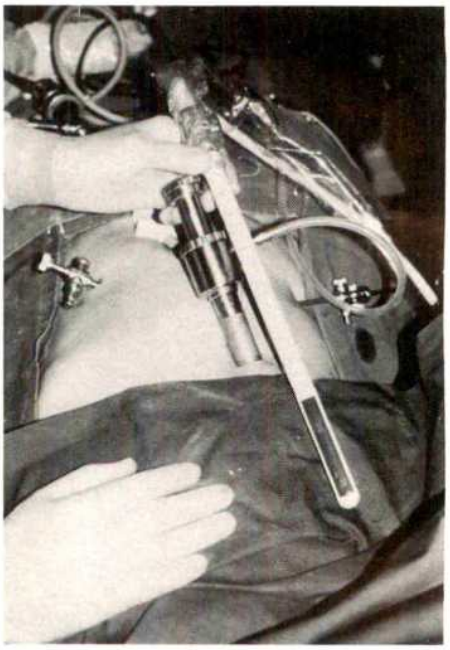

Figure 2 *The 16-mm linear transducer is introduced below the right costal margin in the mid-clavicular line*

Table 1 *Comparison between preoperative diagnosis and that made using laparoscopic ultrasonography in 19 patients with hepatic lesions*

	No. of patients	Diagnosis*		No. of biopsies
		Preoperative	Laparoscopic ultrasonography	
Investigation				
Abdominal pain	2	Undefined (2)	Haemangiomas (1) Carcinoid metastases (1)	1
Breast cancer	3	Metastases (3)	Metastases (1) Haemangiomas (1) Paraganglioma (1)	2
Colorectal cancer	2	Fewer than four metastases (1) More than four metastases (1)	More than four metastases (2)	2
Oesophageal cancer	1	Metastases and cysts	Cysts	0
Liver cancer	3	Irresectable (1) Resectable (2)	Irresectable (2) Resectable (1)	2
Follow-up				
Colorectal cancer	6	Fewer than four metastases (6)	Haemangiomas (1) Cysts (1) More than four metastases (4)	4
Ovarian cancer	1	Metastases	Lipoma	1
Carcinoid syndrome	1	–	Multiple metastases	1

*Values in parentheses are numbers of patients

Hepatic metastases were found during the staging of disease in two patients with colorectal carcinoma, one with a small sigmoid cancer and the other with a rectal tumour. The initial treatment considered for the first patient was resection (fewer than four metastases) and for the second local chemotherapy. During laparoscopic ultrasonography, multiple metastases were found in both patients, with extrahepatic disease in the second. This finding resulted in a change in strategy (no resectional therapy in the first patient and only local palliative treatment of rectal cancer in the second).

In the evaluation of three patients with primary liver cancer, ultrasonography made it possible to determine that the tumour did not involve the left hepatic vein in one. Extended right hepatectomy was subsequently performed. In the other two patients, the tumours were not resectable because of intrahepatic metastases in one and diaphragmatic metastases in the other.

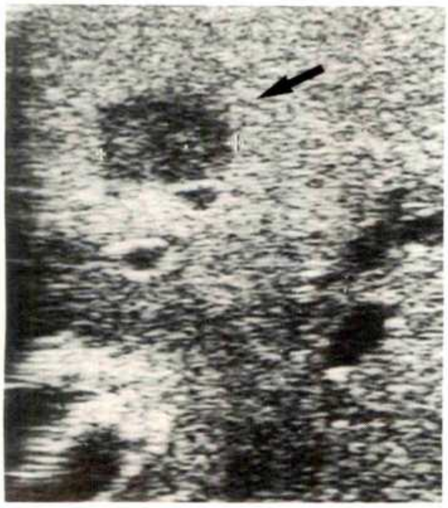

Figure 3 *A 1·5-cm metastasis (arrow) in segment IV, localized using ultrasonography*

Of the six patients in whom liver lesions were found during follow-up for colorectal cancer, multiple haemangiomas were detected in one, multiple cysts in another and multiple liver metastases in the remaining four (peritoneal metastases in two). Because of the large number of metastases, resection was not considered.

In 17 of the 25 patients, biopsy of the lesions (17 liver and two peritoneal biopsies) was performed (*Tables 1* and *2*). Frozen-section studies confirmed the diagnosis in each case.

In the other patients, diagnosis was based on the appearance of the lesion by visualization and ultrasonography (cysts and haemangiomas). The imaging quality of the liver and lesions was very high and the 5-MHz transducer provided a quality equivalent to that obtained by open operative ultrasonography (*Figure 3*).

Of the 19 patients with hepatic lesions, additional information leading to a change in surgical approach was obtained in 16 (*Table 3*). Based on this information laparotomy was avoided in 11 patients and the necessity for resectional therapy confirmed in another four. Of the 16 patients, this additional information was provided in nine by the combination of findings obtained by laparoscopy and ultrasonography, in a further two by laparoscopic visualization of the metastases, and in the remaining five by the information given only by ultrasonography of less obvious lesions.

Three of the five patients with pancreatic cancer had small liver metastases, all of which were visualized by laparoscopy. Ultrasonography of the pancreatic and hepatoduodenal areas was difficult. Although it was possible to ascertain the

Table 2 *Comparison between preoperative diagnosis and that made using laparoscopic ultrasonography in six patients with pancreatic or gallbladder cancer*

	No. of patients	Diagnosis				No. of biopsies
		Preoperative		Laparoscopic ultrasonography		
		Liver	Local tumour	Liver	Local tumour	
Pancreatic cancer						
Head	3	Clear	3 cm	Metastases	3–4 cm Portal vein normal	1
		Clear	2 cm	Clear	4 cm Portal vein normal	0
		Clear	3 cm	Metastases	3 cm Portal vein normal	1
Body	1	Clear	5 cm	Metastases	6 cm	1
Tail	1	Clear	6 cm	Clear	6 cm	0
Gallbladder cancer	1	Resectable		Irresectable (liver metastases)		1

Table 3 *Additional information obtained by laparoscopy and ultrasonography*

	No. of patients	Laparoscopy		Ultrasonography		Laparoscopy plus ultrasonography	
Liver lesions	16 of 19	Multiple metastases (1 carcinoid, 1 breast)	2	Haemangiomas Paraganglioma Lipoma Hepatocellular carcinoma	2 1 1 1	More than four colorectal metastases Multiple cysts Multiple haemangiomas	6 2 1
Gallbladder cancer	1 of 1	Metastases and liver infiltration	1				
Pancreatic cancer	3 of 5	Liver metastases	3				
Total	20 of 25		6		5		9

size of the tumour, no reliable information could be obtained concerning the relation of the tumour to the portal vein and the presence of lymph nodes.

There were no complications related to the procedure and the 12 patients who did not undergo surgical treatment following laparoscopic ultrasonography were discharged the following day. In the eight patients in whom diagnosis was based on the appearance of the lesion, clinical outcome and radiological follow-up have confirmed, so far, the diagnosis made by laparoscopic ultrasonography.

Discussion

Imaging of abdominal organs, especially the liver and retroperitoneum, has improved greatly with the introduction of ultrasonography, CT and MRI. However, these techniques have a sensitivity less than 80 per cent, which is inadequate when very precise information is required for resectional therapy[2,7]. This information may include exact localization and number of liver metastases from colorectal carcinoma or involvement of the portal vein in pancreatic cancer. Furthermore, these techniques are not adequate for the assessment of peritoneal or small liver metastases or lymph nodes, and the surgeon is often faced with a wide discrepancy in diagnoses obtained before and during operation.

The importance of laparoscopic assessment of proximal gastrointestinal malignancies such as those of the oesophagus and gastric cardia, liver and pancreas before a planned laparotomy has been stressed by several authors, who point out[5] that, if these tumours have metastasized, surgery is neither the only nor always the best form of palliative treatment. In the assessment of cancer of the oesophagus and cardia, laparoscopy was found to be more sensitive and accurate than either preoperative ultrasonography or CT with regard to hepatic status (88 *versus* 48 and 56 per cent respectively)[3]. Neither ultrasonography nor CT detected any peritoneal metastases, while laparoscopy detected them in eight of nine cases. The authors concluded that laparoscopy may obviate the need for surgery in some patients with malignant dysphagia. Cuschieri[9] and Warshaw *et al.*[4] have repeatedly shown the value of laparoscopy for staging disease in patients with pancreatic cancer, by obtaining information about small liver and peritoneal metastases. Warshaw *et al.* found this type of metastasis in 22 of 88 patients, metastases that were not found by CT or MRI.

The limitation of laparoscopy lies in the evaluation of less obvious hepatic and retroperitoneal malignancy. Intraoperative ultrasonography was developed to overcome this problem. Rifkin *et al.*[6] found additional information leading to a change in surgical approach in no fewer than 31 per cent of patients with liver tumours. The present authors have obtained similar results[7] using this technique in screening for liver metastases from colorectal cancer. Determining the exact diagnosis of hepatic lesions, their number and precise localization is imperative when considering liver resection or adjuvant therapy. The demonstration of resectability of pancreatic and extrahepatic biliary cancer by intraoperative ultrasonography remains difficult, especially by reason of the encasement and occlusion of the coeliac artery and superior mesenteric and portal veins[10].

A combination of laparoscopy and ultrasonography, using a high-resolution ultrasonographic transducer, is now possible. The use of laparoscopy for inspection of the liver, abdominal cavity and lesser sac, and ultrasonography for the liver and retroperitoneum, can therefore offer significant advantages for the preoperative assessment of these gastrointestinal malignancies. Furthermore, this combination will permit cytological examination and guided biopsies of lesions, and it is even possible to 'palpate' the liver with the laparoscopic instruments.

Yamakawa and Wagai[11] introduced laparoscopic ultrasonography in the evaluation of gallbladder cancer in 1963. Since then, other authors have described similar examinations for the diagnosis of hepatic and pancreatic lesions using linear-array[8,12–14] and sector[15] scanners.

Using a laparoscopic linear-array scanner in the present study, additional information was obtained leading to a change in surgical approach in 16 of 19 patients with liver lesions. In nine of these the information was provided by a combination of data obtained by laparoscopy and ultrasonography, while in a further five with less visible tumours the information was obtained primarily by ultrasonography. Recently, Miles *et al.*[14], using a similar technique with a 5-MHz linear transducer, also found unexpected intrahepatic disease in six of seven patients with hepatic malignancy.

No advantages were derived from the use of the laparoscopic ultrasonography in patients with pancreatic cancer, the additional information for selection of patients for resection being obtained solely by laparoscopic findings. Identification of local resectability in this area will improve with the introduction of 10-mm flexible sector probes with frequencies of 5 and 7·5 MHz and with better understanding and resolution of the ultrasonographic anatomy in this particular area.

Future applications of laparoscopic ultrasonography will include the detection of common bile duct stones during laparoscopic cholecystectomy, liver assessment during laparoscopic resection of colonic cancer, and the precise delineation of renal tumours before laparoscopic resection[16].

Laparoscopic ultrasonography is currently in a preliminary phase of development. It is a simple and reliable technique that will contribute to more accurate preoperative staging of liver and retroperitoneal malignancy.

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Carcinoma of the pancreas and periampullary region: palliation *versus* cure

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A retrospective study of 310 patients with carcinoma of the head of the pancreas or periampullary region was performed. Preoperative bile drainage by placement of a stent reduced the number of postoperative complications, especially bleeding ($P = 0{\cdot}03$)*. The operative mortality rate was nil in patients with periampullary cancer aged under 70 years and 23 per cent in those over 70 years of age* ($P < 0{\cdot}001$)*. In the last 2 years of the study, the mortality rate following resection decreased to 2 per cent. Tumour-containing resection margins did not influence survival after resection* ($P = 0{\cdot}48$)*. Tumour dimension of pancreatic and periampullary cancer and the presence of tumour in locoregional lymph nodes* (N_{1a}) *resected with the primary tumour in cancer of the head of the pancreas were of no prognostic value. Following palliative resection of carcinoma of the pancreatic head, median survival was significantly better than when no resection was performed (10·1* versus *3·9 months,* $P < 0{\cdot}001$)*. In conclusion, even palliative resection may benefit some patients. Preoperative bile drainage is indicated in those with jaundice. Resection should be performed, irrespective of tumour size, provided that the unit's operative mortality rate is sufficiently low.*

In patients with cancer of the head of the pancreas, pancreatoduodenectomy (Whipple's procedure) is the treatment of choice in most centres. However, the tumour proves to be irresectable in many cases and 90 per cent of all patients admitted to hospital with pancreatic cancer die within 1 year. The only chance of prolonged survival lies in radical tumour resection. After surgical treatment with curative intent, a 5-year survival rate of only 0–15 per cent has been found and about 80 per cent of patients die within 2 years of resection. Efforts[1–4] to improve survival by extending the resection to total pancreatectomy or regional extended pancreatectomy as described by Fortner[5] have not met with great success.

The question therefore arises as to whether surgical resection is the best treatment for pancreatic cancer. The operative mortality and morbidity rates are high, and operative risks should be weighed against any expected gain in survival. The operative mortality rate over the years 1981–1986 reported in a recent review of 2398 pancreatic resections from different centres was 16 per cent. Nevertheless, improvement has been made in recent years and even a 0 per cent mortality rate has been reported[6,7].

Operation for cancer of the pancreas can be potentially radical if the malignant process is still confined to the resected area. Before operation an attempt should be made to select patients who have a limited tumour mass without distant metastases or lymph node involvement outside the resection area. At present, no techniques are available to identify such patients accurately. In a previous study[8,9], one general risk factor for operative mortality was identified: patients aged over 70 years had an operative mortality rate of 27 per cent compared with 3 per cent in those less than 70 years of age.

In this study, the results of treatment in 310 patients admitted in the period 1977–1988 were analysed retrospectively to determine the influence of preoperative symptoms, preoperative biliary drainage, tumour size, tumour-containing resection margins and lymph node involvement on the outcome of surgical resection in cancer of the head of the pancreas and periampullary region.

Patients and methods

Between 1977 and 1988, 310 patients were admitted to the Department of Surgery of the University Hospital Dijkzigt, Rotterdam, for cancer of the head of the pancreas or periampullary region. Standard preoperative investigation included ultrasonography, computed tomography (CT), endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) and optional angiography of the coeliac and superior mesenteric arteries.

The mean age of the patients was 62·6 (range 26–89) years. There were 180 men and 130 women. Cancer of the head of the pancreas was diagnosed in 226 patients. No operation was performed in 59 of these patients (26 per cent) because of distant metastases or a bad World Health Organization performance rating. Clinical history, preoperative diagnostic procedures, intraoperative and pathological findings, and follow-up data were analysed using the log rank test, the Cox regression model and Kaplan–Meier life-tables.

The standard operation for resectable cancer was Whipple's procedure. A jejunal loop was used for reconstruction, with end-to-side or end-to-end pancreatojejunostomy with a one-layer inverting running suture. An end-to-side choledochojejunostomy was constructed on the same jejunal loop, also with a one-layer running suture. Stents were not used for the pancreatic duct and in only a few cases for the bile duct. In the case of positive frozen-section examination of the pancreatic resection margin, subtotal or total pancreatectomy was carried out. Pancreatic resection was performed by a limited number of surgeons. Operative mortality was defined as death within 30 days of operation or during the first admission to hospital. Tumour node metastasis (TNM) staging after operation was as defined in the Union Internacional Contra la Cancrum 1987 system, with a modification for the N stage, stage N_{1a} indicating positive lymph nodes within the resection specimen and N_{1b} positive nodes outside the specimen.

Results

Of a total of 242 operations for carcinoma of the head of the pancreas ($n = 167$) or periampullary region ($n = 75$), a radical resection with curative intent could be performed in 106 patients (34 per cent): 50 with cancer of the head of the pancreas (30 per cent resection rate) and 56 with periampullary cancer (75 per cent resection rate). In 19 patients (6 per cent) a

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palliative, i.e. non-radical, resection was performed. Non-radicality was shown after operation by pathological examination: stage T_3 pancreatic cancer (seven patients) and T_4 periampullary cancer (three), N_{1b} (eight) and M_1 (one). Stage T_4 periampullary carcinoma resembles stage T_3 pancreatic cancer, with tumour extending directly to any of the stomach, spleen, colon or adjacent large vessels. In 34 patients with infiltration of tumour into vital organs or distant metastasis to lymph nodes or liver, the operation was limited to an exploratory laparotomy. To treat or prevent biliary or gastric outlet obstruction, a drainage procedure, i.e. choledochojejunostomy and/or gastrojejunostomy, was performed in 83 patients.

Preoperative stent drainage was established by means of PTC or ERCP in 88 patients (39 per cent) with cancer of the head of the pancreas. In 16 patients (7 per cent) stenting was undertaken during operation as a palliative procedure when none had been placed before surgery and no resection was possible. In patients with cancer of the periampullary region, a stent was placed before operation in 28 (33 per cent) and during operation in six (7 per cent). In total, 138 patients (45 per cent) received an endoprosthesis. In 38 patients no treatment other than stenting was possible.

In 40 per cent of all patients (125 of 310) malignancy was cytologically or histologically confirmed before operation.

Patient details

Cancer of the head of the pancreas. Presenting symptoms in 226 patients with carcinoma of the pancreatic head are listed in *Table 1*. Pain, weight loss, jaundice and increased levels of alkaline phosphatase and γ-glutamyl transferase were the main signs. Of patients with pain, distant metastases were found in 97 (62 per cent) during preoperative investigation and, as a consequence, no operation or surgical drainage procedure was performed. Coagulation disorders were all the result of vitamin K deficiency. In 54 patients (24 per cent), tumour size was estimated before surgery by ultrasonography, CT and ERCP; in 15 the tumour was less than 3 cm in diameter.

Table 1 *Preoperative clinical features in patients with cancer of the head of the pancreas or periampullary region*

	Head of the pancreas (*n* = 226)	Periampullary region (*n* = 84)
Pain	157 (69)	40 (48)
Weight loss	173 (77)	57 (68)
Gastric stasis	67 (30)	16 (19)
Jaundice	160 (71)	61 (73)
Altered defaecation	72 (32)	22 (26)
Raised alkaline phosphatase	142 (63)	68 (81)
Raised γ-glutamyl transferase	168 (74)	56 (67)
Raised lactic dehydrogenase	78 (35)	22 (26)
Coagulation disorder	38 (17)	24 (29)

Values in parentheses are percentages

Table 2 *Surgical procedures performed*

	Head of the pancreas (*n* = 226)	Periampullary region (*n* = 84)	Total (*n* = 310)
No operation	59 (26)	9 (11)	68 (22)
Exploratory laparotomy	30 (13)	4 (5)	34 (11)
Drainage procedure	74 (33)	9 (11)	83 (27)
Palliative resection	13 (6)	6 (7)	19 (6)
Curative resection			
Whipple's procedure	30 (13)	41 (49)	71 (23)
PPPD	8 (4)	14 (17)	22 (7)
Total pancreatectomy	12 (5)	1 (1)	13 (4)
Total	50 (22)	56 (67)	106 (34)
Tumour-containing resection margin	9 of 50 (18)	4 of 56 (7)	13 of 106 (12)

Values in parentheses are percentages. PPPD, pylorus-preserving pancreatoduodenectomy

Table 3 *Hospital mortality after operation for pancreatic and periampullary cancer*

	No. of deaths			
		Age (years)		
Site of tumour	Total (*n* = 242)	<70 (*n* = 164)	≥70 (*n* = 78)	*P**
Head of the pancreas				
Overall (*n* = 167)	21 (13)	9 (7)	12 (27)	<0·05
After resection (*n* = 50)	4 (8)	3 (7)	1 (14)	n.s.
Periampullary region				
Overall (*n* = 75)	5 (7)	1 (2)	4 (17)	<0·001
After resection (*n* = 56)	3 (5)	0 (0)	3 (23)	<0·001
Total (*n* = 242)	26 (11)	10 (6)	16 (21)	n.s.

Values in parentheses are percentages. * <70 *versus* ≥70 years (log rank test); n.s., not significant

The surgical procedures performed are shown in *Table 2*. Tumour in the resection margin was found in 20 patients with cancer of the head of the pancreas (11 after palliative Whipple's resection, nine after curative resection).

Cancer of the periampullary region. Eighty-four patients were admitted for carcinoma of the periampullary region, defined as a tumour in the ampulla of Vater (59 patients), distal common bile duct (CBD) (13) or duodenum (12). Weight loss, jaundice and raised levels of alkaline phosphatase and γ-glutamyl transferase were the main presenting features in this group (*Table 1*). Surgical procedures are listed in *Table 2*. Six patients with periampullary cancer had tumour growth in the resection margin (two after palliative, four after curative resection).

Postoperative complications

Cancer of the head of the pancreas. After resection, 14 re-explorations (22 per cent of patients) were needed, ten for intra-abdominal bleeding, one for leakage of the pancreatojejunostomy and three for various reasons. Two wound abscesses were drained on the ward and one intra-abdominal abscess treated conservatively, as were 12 other minor complications. Non-surgical complications (cardiac, respiratory and urinary tract) occurred in 45 patients (27 per cent).

Cancer of the periampullary region. In this group, 14 re-explorations (19 per cent of patients) were carried out, four for intra-abdominal bleeding, two for intra-abdominal abscess, three for leakage of the pancreatojejunostomy and five for other reasons. In one patient, leakage of the pancreatojejunostomy was treated conservatively, as were eight other minor complications. Non-surgical complications occurred in 23 patients (31 per cent).

Preoperative drainage. No preoperative drainage for jaundice was performed in 170 patients; 116 had an endoprosthesis inserted for preoperative biliary drainage. Postoperative laparotomy for bleeding occurred in two patients who underwent stenting before operation and in 14 with no stent ($\chi^2 = 4{\cdot}60$, 1 d.f., $P = 0{\cdot}03$), probably due to disturbance of coagulation as a result of impaired liver function.

Operative mortality

The hospital mortality rate after all surgical interventions was 11 per cent. Patients aged over 70 years had a higher operative risk (*Table 3*). However, this was significant only in overall mortality after all surgical interventions for patients with cancer of the pancreatic head; following resection the difference was not significant. During the last 2 years of study the operative mortality rate after curative resection has fallen to 2 per cent (one patient) in the last 40 procedures.

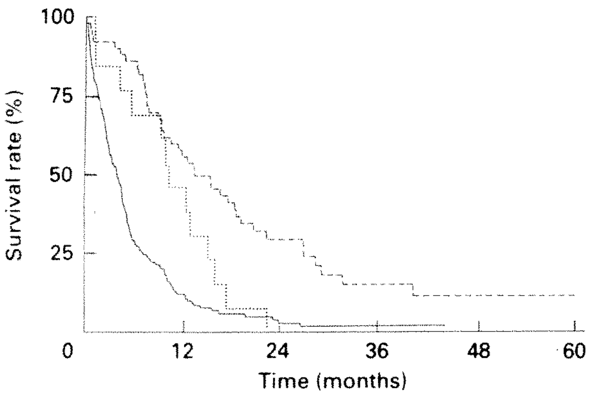
Pathology

Histological investigation of resection specimen margins revealed a high proportion containing tumour, 18 per cent in cancer of the head of the pancreas and 7 per cent in that of the periampullary region. A tumour-containing resection margin was found in five of ten pylorus-preserving pancreatic resections, but no duodenal resection margins containing tumour were found. Almost all tumours were moderately to poorly differentiated adenocarcinoma. In 56 of 78 patients with liver metastases and in 11 of 22 with peritoneal carcinomatosis, histological confirmation of the metastases was obtained.

Survival and prognostic factors

Cancer of the head of the pancreas. Overall survival in this group of patients was 23 per cent at 1 year and 3 per cent at 5 years, with a median survival of 5·1 months. There were significant differences in survival depending on treatment. When no resection was performed, the 1-year survival rate was significantly lower than that in patients undergoing palliative resection (11 *versus* 38 per cent respectively). The longest survival was achieved after intentional curative resection, with survival rates of 56, 28 and 11 per cent at 1, 2 and 5 years respectively (median 13·3 months) (*Figure 1*).

Involvement of local lymph nodes (N_{1a}) did not influence survival after resection with curative intent. In 36 patients with stage N_0 and 14 with stage N_{1a} cancer, a 1-year survival rate of 61 and 35 per cent and a 2-year survival rate of 28 and 20 per cent respectively were observed ($P = 0\cdot43$). Higher age ($P = 0\cdot01$) and pain ($P = 0\cdot003$) were of prognostic value for overall survival in pancreatic cancer, as well as a γ-glutamyl transferase level above 250 units/l ($P < 0\cdot02$) and a lactic dehydrogenase concentration greater than 320 units/l ($P < 0\cdot002$). Tumour dimension measured in the resection specimen directly after operation did not have significant prognostic value. In contrast, tumour size measured before operation showed an unexpected trend ($P = 0\cdot08$): patients with larger tumours had a trend towards improved survival. A positive resection margin was found in 11 patients after palliative and in nine after curative resection. Following resection with curative intent, survival was not influenced by microscopic tumour growth in the resection margin ($P = 0\cdot48$). After multivariate analysis of the prognostic factors significant on univariate analysis, age above 70 years, pain and a lactic dehydrogenase level over 320 units/l remained of significant value for prognosis as independent factors.



No. at risk						
Curative	50	28	14	7	6	6
Palliative	13	5	0	0	0	0
No resection	163	18	3	0	0	0

Figure 1 *Survival related to treatment in patients with cancer of the head of the pancreas.* ——, *No resection;* – – –, *curative resection;* ·····, *palliative resection.* $P < 0\cdot001$ (*log rank test*)

Cancer of the periampullary region. The overall survival rate at 1 year was 65 per cent, at 2 years 45 per cent and at 5 years 28 per cent. Significant improvements in survival were found in this group of patients after both palliative and curative resection compared with no resection ($P < 0\cdot001$). After resection with curative intent, survival rates of 78, 64 and 43 per cent were obtained at 1, 2 and 5 years respectively (median 54·8 months).

There was no difference in survival between 40 patients with stage N_0 and 16 with stage N_{1a} cancer, with a 1-year survival rate of 82 and 65 per cent, a 2-year rate of 70 and 50 per cent, and a 5-year rate of 43 and 42 per cent respectively ($P = 0\cdot43$). However, comparison of survival in these two groups of patients with Greenwood confidence intervals suggests that a significant difference would be found if more patients were included. Age ($P = 0\cdot01$) was a significant prognostic factor for overall survival. Pain ($P = 0\cdot83$) and raised γ-glutamyl transferase ($P = 0\cdot77$) and lactic dehydrogenase ($P = 0\cdot31$) levels had no influence on survival. Tumour-containing resection margins ($P = 0\cdot23$) and tumour size ($P = 0\cdot24$) had no prognostic value. Multivariate analysis showed that only age above 70 years was of prognostic value as an independent factor.

Discussion

Only a small proportion of patients with pancreatic cancer will survive more than 3 years after resection. Apparently the tumour process has metastasized beyond the resection area in most patients at the time of surgery, and this cannot be recognized adequately before or during operation. Better selection criteria are therefore needed to achieve successful curative surgery. In this retrospective study, an attempt has been made to identify variables that might predict outcome or help to select appropriate patients for surgery. The authors accept the limitations of the method, but prospective controlled studies are currently lacking.

The chosen definition of operative mortality is reliable as it includes all deaths related to operation, not only those occurring in the 30-day period. The operative mortality rate after resection was 8 per cent in patients with cancer of the head of the pancreas. The lack of any difference between those aged more or less than 70 years probably reflects careful selection for operation in the older patients. In periampullary cancer in patients aged under 70 years, there were no postoperative deaths, which is significantly different from the mortality rate of 23 per cent found in patients over 70 years of age ($P < 0\cdot001$)[8,9]. The operative mortality rate decreased progressively in the last 2 years of the study to 2 per cent in the most recent 40 resections. A similar low operative mortality rate has been reported by others[7].

Surgical drainage procedures for irresectable tumours carry a high operative mortality rate (about 10 per cent) and should therefore be performed only in the presence of gastric or duodenal obstruction when endoscopic stenting for jaundice is impossible. In this situation, when an operation has to be performed, the addition of gastroenterostomy is advised by some authors[10–13]. The present authors' opinion is that bilioenteric anastomosis should not be combined with gastroenterostomy if the patient has no duodenal obstruction[14].

Preoperative relief of jaundice by stenting the CBD by means of ERCP or PTC resulted in a significant reduction in the number of postoperative laparotomies for bleeding and fewer cases of abscess and anastomotic leakage. Jaundice should be treated as early as possible before operation[9,15]. Resection should be performed only in the non-jaundiced patient.

Non-radical resection was demonstrated in 19 patients by pathological examination, which showed tumour cells in regional lymph nodes outside the resection specimen or even distant metastases. Despite this non-radicality, the prognosis of these patients after palliative resection was significantly better than that in those who underwent surgical drainage or exploratory laparotomy. Resection margins that appeared to contain tumour in the definitive pathological specimen did not appear to influence survival in the present study. Attempts to avoid non-radical resection by extending the area of excision have not been very promising so far[5]. Recently, however, a study from Japan[16] showed significantly reduced local recurrence rates after extended clearance of regional (R_2) lymph nodes.

In the present series of 310 patients admitted for pancreatic or periampullary cancer, potentially curative resection could be performed in only 106 (34 per cent). After curative resection for cancer of the head of the pancreas, 56 per cent of patients survived for more than 1 year, and 2- and 5-year survival rates were 28 and 11 per cent. These survival data are similar to those encountered in other studies[17–26]. In a recent review[6] of 4100 pancreatic resections for cancer, a 5-year survival rate of 4 per cent was found.

In the present study, independent prognostic factors for overall survival were found for patients with cancer of the head of the pancreas. Age above 70 years, pain and a lactic dehydrogenase level greater than 320 units/l correlated with a decreased survival rate. In periampullary cancer, only age above 70 years remained as an independent prognostic factor. In both forms of cancer, tumour size had no prognostic value. Thus, a larger tumour does not necessarily imply a worse prognosis; in the present study, a larger preoperative tumour diameter showed a trend towards a better patient survival rate ($P = 0{\cdot}08$). Tumour infiltration of locoregional lymph nodes (N_{1a}) resected together with the primary tumour did not appear to be of prognostic value in patients with cancer of the head of the pancreas.

In conclusion, pancreatic resection should be performed if technically possible, irrespective of tumour size or infiltration of locoregional lymph nodes (in patients with cancer of the pancreatic head). Non-radical resection may benefit selected patients, especially during the first year after resection. Although the present study suggests that surgical resection for cancer of the head of the pancreas is largely a palliative procedure, curing only a small proportion of patients, it is a good operation in centres with low operative mortality rates. As postoperative morbidity and mortality are increased in jaundiced patients and in those aged over 70 years, preoperative drainage of bile by endoscopic stenting of the distal CBD should be carried out in patients with jaundice and great caution is advised in the elderly.

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Pancreatic necrosis: assessment of outcome related to quality of life and cost of management

Ten patients with necrotizing pancreatitis admitted consecutively between August 1990 and August 1991 were studied. They comprised eight men and two women of median age 63 (range 29–73) years. One patient died. The median length of hospital stay was 74 (range 40–150) days. The median number of operations and endoscopic procedures performed per patient was 4 (range 2–7). Investigations performed included multiple bacteriological, radiological, haematological and biochemical tests. The mean cost of management was £18 441 (range £9296–£33 796), of which hospitalization accounted for 65 per cent, operations and endoscopic procedures 20 per cent and investigations 16 per cent. Cost–utility analysis demonstrated a mean benefit per patient of 8·55 quality-adjusted life years gained at a cost of £2157 each. The management of pancreatic necrosis is expensive but justified by the excellent outcome in terms of quality of life.

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Acute necrotizing pancreatitis is associated with significant morbidity and mortality rates. The incidence of this type of acute pancreatitis varies from 4 to 18 per cent; the condition has a reported mortality rate of 9–40 per cent[1–9].

Management of acute necrotizing pancreatitis includes full conservative (supportive) therapy and repeated clinical evaluation requiring multiple haematological, biochemical, bacteriological and radiological investigations. Successful outcome usually involves major surgery and a prolonged hospital stay involving the intensive therapy unit and high-dependency care[1,3,5–9]. Improvements in management have led to a reduction in mortality rates, particularly in specialized units where technical resources and experienced personnel are available. Pancreatic necrosectomy and packing[7] or continuous peritoneal lavage[1] forms the mainstay of surgical treatment. The advent of bolus intravenous contrast-enhanced computed tomography (CT) has enabled better delineation of pancreatic necrosis and, together with percutaneous aspiration of potentially infected necrosis, has aided in determining the extent and timing of surgery[10,11].

Treatment becomes increasingly expensive as more sophisticated and invasive procedures are used and there is a need for critical assessment of outcome with respect to the resources required for successful management. Cost analysis will benefit patient care in supporting the case for adequate funding of units specializing in the management of this condition.

There is accumulating evidence that quality-of-life measurements may be a more sensitive means of assessing outcome than crude survival rates[12]. Several methods have been validated for assessing quality of life[13]. A standard unit termed a quality-adjusted life year (QALY) can be obtained when quality of life is related to life expectancy[14,15]. A QALY represents 1 year of healthy life expectancy gained after treatment. The aim of the present study was to determine the cost of treatment and relate this to outcome in terms of quality of life.

Patients and methods

Patients

The medical records of ten consecutive patients admitted between August 1990 and August 1991 who required operative intervention for pancreatic necrosis were reviewed. All patients were managed by a team of medical, nursing and paramedical staff. Multiple clinical and laboratory data were obtained from patient records. The severity of acute pancreatitis was assessed objectively using the Glasgow system[16] and the aetiology determined from clinical findings in all patients. Bolus intravenous contrast-enhanced CT was performed on all patients. Pancreatic necrosis was confirmed histologically in each patient and the type of infection determined before surgery by percutaneous aspiration or from cultures of the necrosectomy specimens. Patients were seen regularly in the follow-up clinic for up to 2 years after treatment.

Methods

Cost. The cost of management was based on budget estimates made by the Greater Glasgow Health Board for the period April 1991 to March 1992 (personal communication). The cost and services provided for each patient were summarized in three parts: hospitalization, operations, and procedures and investigations. Hospitalization costs included elements for nursing and medical staff, pharmacy, physiotherapy and other support services, catering, administration plus maintenance and service charges. The cost was

Table 1 *Individual costs of services*

Service	Cost (£)
Hospitalization	
Standard ward bed (per day)	75
Intensive care bed (per day)	635
Operations and procedures	
Operating theatre time (per min)	10
Endoscopic retrograde cholangiopancreatography	300
Endoscopy	200
Investigations	
Full blood count	15
Bacteriology	22
Biochemistry	10
Chest radiography	13
Abdominal computed tomography	66
Abdominal ultrasonography	30
Abdominal radiography	12
Sinography	16
Barium meal	28
Venography	51
Barium enema	60
Aortic angiography	100
Lumbosacral spine radiography	28
Foot radiography	17
Hand radiography	17

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calculated by multiplying the number of services provided by the cost of each service. The number of services provided was obtained from patient case notes, and operating theatre, radiology department and intensive care records. A cost for endoscopic procedures was not available from the Health Board, so an estimated cost for endoscopic retrograde cholangiopancreatography (ERCP) and upper gastrointestinal endoscopy is given (*Table 1*).

Quality of life. Quality of life was determined using the Rosser disability and distress index[15] at admission and follow-up. This was performed by the senior surgeon who graded patients according to *The QALY Toolkit*[17]. QALYs were derived from the difference in quality of life levels following treatment related to life expectancy. Assumptions made in the calculation of QALYs were that patients would have died without treatment and, having survived, would have a normal life expectancy of 75 years. A 5 per cent annuity factor was used to determine the current value of QALYs gained. The cost of treatment was then related to the number of QALYs gained to give a cost per QALY.

Results

Patients

The ten patients comprised eight men and two women of median age 63 (range 29–73) years (*Table 2*). The aetiology was gallstones in seven patients and alcohol in three. The Glasgow score[16] was 3 or above for all patients, predicting severe pancreatitis; the median score was 4 (range 3–5). The median hospital stay was 74 (range 40–150) days and that in the intensive therapy unit 7 (range 2–29) days. Bolus intravenous contrast-enhanced CT revealed pancreatic or peripancreatic necrosis in all ten patients. Six of the ten had infected pancreatic necrosis, five of whom had gallstone pancreatitis. Seven patients underwent peritoneal lavage after initial debridement; packing of the pancreatic bed was employed initially in three patients. One 66-year-old patient died from Gram-negative septicaemic shock, giving a mortality rate of 10 per cent. On follow-up at 1 year a further patient had died from a cerebrovascular accident.

Cost

The cost and services provided for each patient treated are summarized in *Table 3*. The mean cost of hospitalization was £11 898 (range £4680–£25 540), representing 65 per cent of the total cost. Operations and endoscopic procedures accounted for 20 per cent of the total cost of management. The median number of operations performed per patient was 2 (range 1–4). The operating time for pancreatic necrosectomy, cholecystectomy and feeding jejunostomy was approximately 3 h. The median operating time for pancreatic necrosectomy was 2 h, costing £1200. The mean cost of operations per patient was £3270 (range £1800–5700). The median number of endoscopic procedures performed per patient was 1 (range 0–4). The cost of endoscopic procedures per patient ranged from £0 to £900, with a mean of £400. Investigations performed represented 16 per cent of the total cost with a mean of £2864 per patient. The mean total cost per patient treated was £18 441 (range £9296–£33 796) (*Table 3*).

Table 2 *Summary of clinical details*

Patient no.	Age (years)	Sex	Aetiology	Glasgow score†	Infected pancreatic necrosis	Organisms cultured
1*	66	M	Gallstones	3	+	*Klebsiella* sp., *Candida albicans*
2	43	M	Alcohol	4	+	*Escherichia coli*, *Streptococcus faecalis*
3	64	F	Gallstones	3	+	*Escherichia coli*
4	59	M	Gallstones	3	+	*Escherichia coli*, *Staphylococcus aureus*
5	72	M	Gallstones	5	+	*Staphylococcus aureus*
6	70	M	Gallstones	5	+	*Clostridium welchii*, *Klebsiella* sp.
7	32	M	Alcohol	4	–	–
8	62	M	Gallstones	3	–	–
9	29	M	Alcohol	4	–	–
10	73	F	Gallstones	4	–	–

*Patient died. †Score $\geqslant 3$ predicts severe pancreatitis[16]

Table 3 *Summary of services provided and costing*

	Hospitalization			Operations and procedures			Investigations					
	Stay (days)			No.			No.					
Patient no.	Ward	ITU	Cost (£)	Operations	Procedures*	Cost (£)	FBC	Biochem.	Bact.	Radiog.	Cost (£)	Total cost per patient (£)
1	49	2	4945	3	1	3500	17	64	21	18	1851	10 296
2	111	14	17 215	4	1	6000	41	156	51	38	4115	27 330
3	71	2	6595	2	2	4200	26	100	33	12	2479	13 274
4	69	2	6445	2	0	3000	23	88	29	17	2255	11 700
5	52	17	14 695	2	1	3900	22	85	27	35	2501	21 096
6	95	29	25 540	2	3	3800	41	155	50	50	4456	33 796
7	146	4	13 490	1	1	2100	17	169	61	21	3811	19 401
8	37	3	4680	2	1	3200	13	50	16	15	1416	9296
9	61	13	12 830	1	2	2300	25	93	31	22	2454	17 584
10	91	9	12 540	3	4	4800	33	125	41	28	3298	20 638
Total			118 975 (65)			36 800 (20)					28 636 (16)	184 411 (100)
Mean			11 898			3680					2864	18 441

Values in parentheses are percentages. *Procedures include endoscopic retrograde cholangiopancreatography and upper gastrointestinal endoscopy. ITU, intensive therapy unit; FBC, full blood count; Biochem., biochemistry; Bact., bacteriology; Radiog., radiography

Table 4 *Calculation of quality-adjusted life years utilizing 5 per cent annuity discount factor*

Patient no.	Age (years)	Sex	Life remaining (years)	Quality of life		QALYs gained	QALYs gained (5% discount factor)†
				Level	Score		
1*	66	M	0	VIIIA	0·000	0	0
2	43	M	32	IIA	0·990	31·68	15·45
3	64	F	11	IIA	1·000	11·00	8·31
4	59	M	16	IIIA	0·980	15·68	10·62
5	72	M	1	VIC	0·680	0·68	0·65
6	70	M	5	IA	1·000	5·00	4·33
7	32	M	43	IA	1·000	43·00	17·55
8	62	M	13	VB	0·956	12·43	8·98
9	29	M	46	IA	1·000	46·00	17·89
10	73	F	2	VB	0·935	1·87	1·74
Total						167·34	85·50

*Patient died. †The mean quality-adjusted life years (QALYs) gained per patient was 8·55 (applying 5 per cent discount factor)

Quality of life

A summary of the quality of life and the QALYs gained by each patient treated is given in *Table 4*. The mean gain per patient was 8·55 QALYs (applying 5 per cent discount) with a mean cost per patient treated of £18 441, giving a cost for each QALY gained of £2157.

Discussion

The ten patients in this limited series are similar to those in most other studies regarding aetiology of pancreatitis, male preponderance and incidence of infected necrosis[1,4,5,7–9,18]. However, the median age of 63 years in the present series is older than that reported by others (median age range 39–54 years)[1,7–9,18,19].

Costs were divided into three main components to facilitate analysis. Hospitalization is the ward cost for each patient and accounted for 65 per cent of the total expenditure. This included costs of staff, pharmaceuticals, physiotherapy and other support services. The lengthy hospital stay of 40–150 days reflects the severity of the disease and the debilitated state of patients. The incidence of complications is known to increase with more invasive procedures and increased hospital stay[20]. Expensive nutritional supplementation in the form of total parenteral nutrition and enteral feeding is required for patients with acute necrotizing pancreatitis as they are catabolic for long periods of the illness and often suffer from prolonged ileus. Despite the lengthy hospital stay the time spent in the intensive therapy unit was relatively short (median 7 days), similar to the finding of others[1]. Good-quality high-dependency care in the ward helps to shorten the stay in an intensive therapy unit.

Theatre time is expensive and patients may require several operations and endoscopic procedures. These accounted for 20 per cent of the total cost of management. Although operating costs were accurately known, the cost of endoscopy and ERCP were estimated. A 50 per cent error in this estimation would increase the total by 1 per cent.

Investigations accounted for 16 per cent of the total expenditure. This area presents a potential for cost savings by restricting the tests ordered to those that alter management (*Table 2*). Some would say that costing is outside the clinician's remit, a view with which we would tend to agree. However, the ability of the healthcare system to optimize the available resources is reliant on the cooperation of clinicians. Awareness of the cost of treatment has been shown to lead to better utilization of resources without compromise of patient care[21,22].

The 10 per cent mortality rate in this series is encouraging and compares favourably with the experience of other centres. The Rosser index is a measure of quality of life based on the degree of disability and distress that a patient experiences. Disability and distress when combined give an accurate level of disease severity that has been validated in previous studies[15,23]. The levels are given a numerical score from 0 to 1, 0 representing severe illness or death and 1 perfect health. The difference in values following therapy gives a measure of the benefit gained from treatment. This is then related to the patient's life expectancy to derive QALYs gained (*Table 4*). An actuarial discount factor of 5 per cent was applied to future QALYs gained as this was thought to reflect the changing value of the gain from the patient's viewpoint with time.

A cost–utility analysis was also performed; this is a special type of cost–effectiveness analysis expressed in terms of QALYs[14]. This method has several advantages over cost–effectiveness analysis. Outcome when expressed in terms of a standard unit can be used as a tool for comparing and improving the quality of care delivered by different regimens for the same or dissimilar conditions[24]. In broader terms it may aid in the selection of patients for surgery and may help in making policy decisions regarding management[25,26]. In an era of cost consciousness where the healthcare budget is limited this can serve as a useful guide to resource allocation to obtain maximum benefit[27].

The present patients have shown a mean benefit of 8·55 QALYs at a cost of £2157 each. This is similar to the benefit of coronary artery bypass grafting at around £1500 per QALY gained and is more favourable than that of kidney transplantation at £6072 per QALY gained (1988 prices)[28,29]. These figures indicate that the substantial costs involved in managing patients with pancreatic necrosis result in a worthwhile gain in quality of life.

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Good long-term results in patients surviving severe acute pancreatitis

Thirty-seven patients treated for severe acute pancreatitis were investigated a mean of 6·2 years after the attack; 30 were found to be in good condition and 24 were working normally. Two-thirds of previously heavy drinkers had either reduced their intake considerably or become abstainers. The main complication observed on follow-up was diabetes mellitus, which affected 20 patients and required insulin treatment in nine. Of the remaining patients, four were taking oral antidiabetic agents and seven were on a strict diabetic diet. Before severe acute pancreatitis none had been diabetic. All patients who underwent resection of the pancreas developed diabetes. In 21 of 24 patients with overt or imminent diabetes, pancreatitis had been primarily alcoholic in origin. Polyneuropathy, as diagnosed by clinical signs and/or neurophysiological tests, was observed in six patients, all of them heavy drinkers. It is concluded that patients with severe acute pancreatitis have a high chance of returning to normal activity and productive work. These results serve to encourage all those involved to persist with the exacting work involved in treating such patients.

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Severe acute pancreatitis always requires intensive care. In many cases such care proves insufficient and it may be necessary to resort to peritoneal lavage or pancreatic resection. Both have been maintained to be superior to conservative treatment alone[1–6], although conflicting views have also been expressed[7]. Nowadays, debridement of necrotic tissue is perhaps the commonest operative treatment[8]. The primary results of various therapies were reviewed in 1986 by Hollender *et al.*[9]. Very few recent reports have been published. Nordback and Auvinen[10] noted a 92 per cent incidence of diabetes in patients who had undergone pancreatic resection. An unexpected finding was a high incidence of peripheral neuropathy, which affected 42 per cent of patients. Gross *et al.*[11] reported four patients with partly reversible polyneuropathy associated with pancreatitis and pancreatic pseudocyst.

One aim of the present study was to determine the outcome for patients surviving severe acute pancreatitis, especially in relation to the incidence and type of complications. According to the authors' practice[3], peritoneal lavage was used as a primary treatment for acute pancreatitis and only those who did not recover (one-third of patients) underwent pancreatic resection; the influence of operative treatment on outcome was also evaluated.

Patients and methods

Between 1974 and 1988, 67 patients with severe acute pancreatitis were treated in the intensive care unit. Severe acute pancreatitis is defined by the presence of multiple organ failure in patients with haemorrhagic and/or necrotic pancreatitis. Diagnosis was based mainly on clinical findings: all patients had abdominal pain, serum amylasaemia and abdominal tenderness on palpation concomitant with a markedly poor general condition. Dynamic sequential computed tomography (CT) and ultrasonography were undertaken, but results were not decisive in relation to treatment. The main indications for laparotomy were peritonitis, renal failure despite aggressive fluid management, respiratory failure, shock, mental confusion and severe ascites. In most patients two such conditions were recorded, as reported previously[2]. The diagnosis was confirmed at laparotomy, carried out primarily or after unsuccessful conservative treatment. In all patients there were varying amounts of discoloured ascitic fluid. Yellow fatty saponification spots were abundant in the mesentery or around the pancreas in all patients. The pancreatic body and tail were exposed through the lesser sac. The gastrocolic ligament was opened to allow thorough inspection of the pancreas. The head of the gland was exposed from the right by means of an enlarged Kocher manoeuvre. If necessary, the pancreas was inspected from below by opening the mesocolon. The gland appeared haemorrhagic or necrotic in all subjects but no biopsies were taken.

Primary treatment included peritoneal lavage in all cases. In the first three patients, catheters were inserted by means of abdominal puncture. The other patients were subjected to laparotomy as described above and catheters placed around the pancreas. If the general condition deteriorated despite such conservative treatment the patient underwent a further laparotomy and pancreatic surgery. In six patients the body and tail were resected and in six subtotal (80 per cent) pancreatectomy performed. The line of resection was determined by the appearance and vascularization of the right part of the pancreas. One patient underwent surgery again 2 years after the attack of severe acute pancreatitis because of chronic pancreatitis; total pancreatectomy was performed.

Of the 67 patients, 23 (34 per cent) died in hospital. Of the 44 survivors, four died after discharge; the mean age at death was 52 (range 38–65) years. Three had suffered from alcohol-related severe acute pancreatitis and one from pancreatitis of unknown origin. All had been treated by lavage and none had undergone resection. One of the four had diabetes, which had been treated by oral medication before pancreatitis developed. Another developed diabetes 7 years after operation. One man succumbed to massive recurrent severe acute pancreatitis. The deaths of the others were not related to pancreatitis.

Three patients could not be contacted for follow-up. The final follow-up examination thus included 37 subjects. According to Ranson's criteria, 60 per cent of the patients who underwent resection compared with 53 per cent of those receiving lavage alone had suffered severe pancreatitis.

Patients were interviewed a mean of 6·2 (range 1–14) years after the attack of pancreatitis. General condition, abdominal or other symptoms, working capacity and alcohol consumption were determined. Patients were examined, with special emphasis on abdominal and neurological status. Those with overt neurological symptoms underwent thorough clinical neurological examination and neurophysiological studies, including electroneuromyography, electroencephalography and CT of the brain.

Laboratory tests included determination of haemoglobin concentration and leucocyte count, and measurement of serum amylase, serum alanine aminotransferase and serum glutamyltransferase levels. Concentrations of blood glucose, C peptide, and of glycohaemoglobin A_1 and A_{1c} were determined. An oral glucose tolerance test was conducted in most non-diabetic patients with fasting blood glucose level below 7 mmol/l. The patients were given a 75-g oral glucose load after a 12-h overnight fast.

The level of alcohol consumption was determined from interview findings and records from nearby hospitals. Patients were classified as

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abstinent if they did not drink; drinking was moderate if the patient took alcohol occasionally and heavy if drinking was almost daily or if there were social or psychological problems arising from alcohol abuse.

Statistical analysis

Statistical analysis was performed using the χ^2 test with Yates' correction when needed and Fisher's exact test. $P < 0{\cdot}05$ was considered significant.

Results

A total of 37 patients comprising 25 men and 12 women of mean age 49 (range 26–90) years were re-examined. Severe acute pancreatitis had been induced by alcohol (heavy drinking) in 28 patients. The cause was biliary in three patients, endoscopic retrograde cholangiopancreatography in two and unknown in four.

Table 1 shows social status and working capacity before pancreatitis and on follow-up. All but one patient had been in normal general condition before falling ill. At follow-up, general condition was found to be normal in 30 of the 37 patients.

At the time of their illness, 31 patients had been working, four had retired because of age and two because of illness (in one case psychiatric problems, in the other cardiac disease). At follow-up, patients' working capacity remained good (*Table 1*). Only four had retired as a result of complications of pancreatitis. Two had continued to drink heavily and had evidence of liver damage and neurological symptoms. One of the four had retired because of postoperative herniation, diarrhoea and spinal problems, and one because of major hernias and poor general condition at age 60 years. One was unemployed, partly because of drink problems.

Of the 28 patients whose pancreatitis was alcohol related, 11 had become abstainers, seven drank only moderate amounts and ten still had a serious drink problem.

Table 1 *Clinical findings in 37 patients*

	Before pancreatitis	At follow-up*
General condition		
Normal	36 (97)	30 (81)
Poor	1 (3)	7 (19)
Working capacity		
Normal	31 (84)	24 (65)
Reduced	0 (0)	2 (5)
Retired		
Age	4 (11)	4 (11)
Illness	2 (5)	3 (8)
Pancreatitis	0 (0)	4 (11)

Values in parentheses are percentages. *Follow-up was a mean 6·2 years after severe acute pancreatitis

At follow-up, eight patients exhibited neurological symptoms; all had diabetes. Six complained of numbness in the legs, of whom four were subjected to electroneuromyography. All six had suffered from alcohol-induced pancreatitis. One man who had undergone pancreatic resection had continued to drink heavily. Polyneuropathy was reflected in an abnormal electroneuromyograph. CT of the brain revealed atrophic changes in the cerebellum; these are usually related to alcohol abuse. Two women treated with peritoneal lavage were still drinking heavily. Both exhibited polyneuropathy, one also had cerebellar atrophy and they had difficulties in walking. A further three complained of numbness in the legs but only one underwent electroneuromyography, which showed polyneuropathy.

One patient had been drinking heavily before the attack of acute pancreatitis and had unknowingly suffered neurological symptoms. CT revealed atrophic changes in the cerebellum. The patient is now an abstainer. One patient had developed hemiplegia during primary hospitalization. The extremities on the affected side were still spastic at follow-up. No explanation for the hemiplegia was found on examination by brain CT or electroencephalography. Three patients with polyneuropathy also had diarrhoea.

Before presentation with severe acute pancreatitis no patient had diabetes. On discharge from hospital 11 of the 37 suffered from diabetes; six were being treated with insulin, one with sulphonylurea and four were on a strict diabetic diet. At follow-up, 20 patients had diabetes; nine were being treated with insulin, four with sulphonylurea and seven were on a strict diet (*Table 2*). Of 17 patients who were not diabetic, four had impaired glucose tolerance as indicated by results of oral glucose tolerance tests.

All 13 patients who had undergone resection of the pancreas developed diabetes compared with only seven of the 24 treated conservatively ($P < 0{\cdot}005$). Of 28 patients whose pancreatitis was alcohol related, 18 had diabetes. Of patients in whom the pancreatitis was not alcohol related, only two had diabetes ($P < 0{\cdot}05$).

The commonest major complications were abscess, fistula and pseudocyst. These occurred in 22 patients. There was no correlation between the appearance of major complications and development of diabetes.

Fourteen patients experienced abdominal complaints, mostly minor dyspepsia or abdominal fullness after eating a fatty meal. Six had diarrhoea, two of whom were permanently disabled because the diarrhoea was resistant to therapy. All patients with diarrhoea also had diabetes ($P < 0{\cdot}05$); five of these exhibited no clear clinical signs of chronic pancreatitis in that severe, constant abdominal pain and weight loss were absent. One patient with clear symptoms of chronic pancreatitis

Table 2 *Diabetes and treatment after severe acute pancreatitis*

		Diabetes		
	No diabetes	Dietary treatment	Oral antidiabetic agents	Insulin treatment
Diabetic status				
Before pancreatitis	37 (100)	0 (0)	0 (0)	0 (0)
Immediately after pancreatitis	26 (70)	4 (11)	1 (3)	6 (16)
At follow-up	17 (46)	7 (19)	4 (11)	9 (24)
Diabetic status at follow-up in relation to treatment				
Lavage ($n = 24$)	17 (71)	4 (17)	1 (4)	2 (8)
Resection ($n = 13$)	0 (0)	3 (23)	3 (23)	7 (54)
Diabetic status at follow-up in relation to aetiology of pancreatitis				
Alcohol ($n = 28$)	10 (36)	7 (25)	4 (14)	7 (25)
Other ($n = 9$)	7 (78)	0 (0)	0 (0)	2 (22)

Values in parentheses are percentages

who underwent total pancreatectomy 18 months after the primary attack of pancreatitis had disease of unknown origin.

The only significant difference in the results of serum biochemical tests between patients who had undergone resection and those treated conservatively was related to diabetes.

Discussion

Severe acute pancreatitis has a high mortality rate of 13–64 per cent[9,10,12–15]. Treatment is extremely laborious, time consuming and costly, involving long periods in an intensive care unit and in the hospital ward and, often, prolonged convalescence. Its utility may be questioned. However, the long-term outcome in the present study was good. Of 37 patients followed up, 30 were in good general condition and 24 were working to full capacity, compared with 31 before the attack. Working capacity after severe acute pancreatitis has rarely been mentioned in previous reports although Nordback and Auvinen[10] found it to be less than in the present study. The difference could be related to types of occupation.

The small percentage of patients found to be heavy alcohol drinkers at follow-up was surprising. It was gratifying to find that two-thirds of subjects had reduced their alcohol consumption. Although no blood alcohol concentrations were measured in connection with re-examination, complications of heavy drinking were sought, partly by reference to county hospital files. Those continuing to drink heavily paid numerous visits to hospital, especially to outpatient clinics.

The main long-term complication of severe acute pancreatitis was diabetes. It usually occurred in patients who had undergone pancreatic resection after failure of peritoneal lavage, and not because of major complications. It is possible that the attack of acute pancreatitis was more severe from the outset in these patients, so that the pancreas had consequently been more damaged. However, no clear evidence was found to support this contention. There are no specific clinical or laboratory parameters that correlate with the extent of necrosis[16].

The present incidence of diabetes was higher than that found in previous studies[3,9,10,12], apparently because of the longer follow-up. A high incidence of diabetes (92 per cent) after pancreatic resection was also found in one other study in which the follow-up was lengthy[10]. Oral glucose tolerance testing showed that four further patients in the present study had impaired glucose tolerance; they were included in the non-diabetic group but will probably develop diabetes[17].

Diabetes after severe acute pancreatitis, especially following pancreatic resection, has been noted by others[3,4,9,10,12,18]. Since the present patients showed no overt signs of chronic pancreatitis[19,20] or markedly decreased liver function that could explain the results, a direct toxic effect of alcohol on pancreatic islets seems possible. During the past few years there has been a tendency to avoid pancreatic resection[21–23]. If surgery is unavoidable, necrosectomy has been advocated[16,24,25]. Pancreatic necrosis as such is not an absolute indication for surgical treatment but, if necrotic tissue is infected, the patient cannot be managed by conservative treatment and operation is usually necessary[26]. Good results have also been achieved with relaparotomy at intervals of 2–3 days (open drainage)[27].

The present study could not verify the high frequency and severity of polyneuropathy (42 per cent) noted by Nordback and Auvinen[10]. Of 37 patients only four cases of polyneuropathy were verified by electroneuromyography. Gross *et al.*[11] have suggested that polyneuropathy associated with pancreatitis is a consequence of insufficient parenteral nutrition, multiple drug therapy (including use of metronidazole) and sepsis as seen in other critically ill patients, or that it is a specific distinct disease. All patients with verified abnormal electroneuromyograms were heavy drinkers. It would seem that polyneuropathy was predominantly alcohol related, as indicated by cerebellar atrophy shown by brain CT, rather than a direct effect of diabetes. Furthermore, the time from the attack of pancreatitis to onset of neurological symptoms seems too short for the development of diabetic polyneuropathy. The heavy drinkers were in poor nutritional condition before the attack. This, together with a possible toxic effect of alcohol, could perhaps explain the polyneuropathy. Patients with normal glucose tolerance test results exhibited no signs of polyneuropathy.

This follow-up study has shown generally good outcome for patients who survive an attack of severe acute pancreatitis. General condition and working capacity were well maintained in the majority. Two-thirds of the patients stopped drinking heavily. The main problem arising after acute pancreatitis was diabetes, the incidence of which increased with time. Diabetes was commoner after operative treatment. It will be interesting to study late results after necrosectomy. We recommend conservative treatment whenever possible. This study supports our belief that patients with severe acute pancreatitis are definitely worth treating.

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Announcement

European Surgical Fellowships

The Council of *The British Journal of Surgery* is pleased to announce the availability of European Surgical Fellowships for 1994. Last year four Fellowships were awarded, to Dr Jose Luis Aguayo-Albasini (Spain), Mr R. M. Charnley (Nottingham), Mr S. D. Heys (Aberdeen) and Mr T. G. John (Edinburgh).

It is Council's intention to offer European Surgical Fellowships again in 1994. Each Fellowship will have a value of up to £3000 and is intended to allow surgeons working in the UK to visit centres in other European countries or surgeons working in other European countries to visit the UK. Applicants must be under 40 years of age and should submit details of their proposed itinerary and its anticipated cost, together with a copy of their *curriculum vitae* and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, by 1 February 1994.

D. C. Carter

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Early discharge after operation

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To assess the feasibility and advantages of short-stay surgery in India, a policy of early discharge was adopted for 386 patients undergoing various major and minor operations. The mean postoperative and total hospital stays of patients admitted for minor surgery were 1·9 and 3·7 days respectively; the corresponding figures for age- and sex-matched historical controls were 7·4 and 11·3 days. The mean postoperative and total stays of patients who had undergone major surgery were 4·1 and 8·0 days respectively; the corresponding control values were 8·9 and 12·5 days. The use of absorbable subcuticular skin sutures helped to shorten postoperative hospital stay and avoided an extra follow-up visit. The overall complication rate in the study group was 9·6 per cent and in historical controls 13·4 per cent ($\mathrm{P} > 0{\cdot}05$). A total of 2357 hospital bed-days were saved during the study and 95·6 per cent of patients approved of short-stay surgery.

Shortening hospital stay has several advantages. The cost of treatment decreases[1–3] because inpatient treatment is more expensive than outpatient care. Hospital beds, which are expensive to maintain and limited in number, are made available to other patients, thus cutting waiting lists and reducing sick-leave absenteeism[3–5]. Universal adoption of a policy of early discharge could do much to ease the load on the overburdened Indian medical system. However, convalescence at home increases the responsibility of family practitioners and community nurses[6–8], and requires good transport and referral systems, services unavailable to most Indians. In the event of a complication or emergency occurring after discharge, timely medical care would probably be inaccessible. This work was undertaken to study the feasibility and safety of short-stay surgery in India.

Patients and methods

The study was conducted in two phases. The first involved 200 consecutive patients due to have minor operations who were aged between 10 and 60 (mean 31·9) years (male:female ratio 1:0·47) and living close to the hospital. All consented to inclusion in the study. Patients were investigated on an outpatient basis and admitted to hospital on the morning of surgery for the operations shown in *Table 1*. After surgery, patients were discharged when they had recovered from anaesthesia and vital signs were stable. They were called for follow-up 3 and 7 days after discharge and they and their families were given questionnaires to assess opinions about short-stay surgery. These 200 patients were compared with 200 age- and sex-matched historical controls (mean age 33·6 years, male:female ratio 1:0·50) with similar surgical problems and who had undergone similar operations.

After success in the first phase, the second phase included patients due for routine major surgery; those undergoing more extensive operations such as oesophagectomy, Whipple's procedure and so forth were excluded. Some 186 patients of age 10–65 (mean 37·3) years (male:female ratio 1:1·16) were considered appropriate for early discharge after the operations shown in *Table 2*. Twenty patients had associated disease requiring specific treatment but not delaying discharge: ten were hypertensive, two had coronary or rheumatic heart disease, one was diabetic, three had pulmonary tuberculosis and four had a variety of miscellaneous problems. The 186 patients were investigated on an outpatient basis and admitted and subjected to surgery on the first available operating day. They were discharged when bowel function returned to normal and adequate oral intake was achieved, provided no significant complication had occurred. Those with drains *in situ* were not discharged and nasogastric decompression was routine after laparotomy. With these considerations in mind, the following limits were adopted to define short stay after surgery: thyroid, biliary and urogenital surgery – 4 days; mastectomy – 6 days; and gastrointestinal surgery – 7 days. Patients were called for follow-up at 1 week and 1 month after discharge. Polyglactin suture for subcuticular skin closure obviated the need for an extra hospital visit for suture removal. At the 1-month visit the questionnaire was used to assess opinion on short-stay care. The performance of these patients was compared with that of 180 historical controls operated on by the same unit in the year preceding the study. Control patients were matched as far as possible for age (mean 38·9 years) and sex (male:female ratio 1:2·95). Test and control patients belonged to similar diagnostic categories and underwent similar operations; 18 of the control patients had associated medical problems similar to those of the 20 test patients.

Table 1 *Operations on patients in phase 1*

	No. of patients
Hernia repair	75
Hydrocelectomy, orchidectomy or testicular biopsy	24
Interval appendicectomy	18
Hemithryoidectomy	18
Salivary gland excision	16
Breast lump excision	15
Laparoscopy	4
Miscellaneous	30
Total	200

Table 2 *Operations on patients in phase 2*

	No. of patients
Thyroidectomy	31
Mastectomy	34
Cholecystectomy	47
Appendicectomy	21
Bowel surgery	19
Urological surgery	27
Miscellaneous	7
Total	186

Patient care standards were not compromised at any stage. Apart from the use of absorbable subcuticular sutures for skin closure, surgical and anaesthetic techniques were not altered to facilitate early discharge.

Results

Phase 1

The 200 patients were admitted to hospital on the morning of scheduled surgery, but unforeseen factors such as non-availability of operating time caused the postponement of some operations. Affected patients usually chose to stay in hospital

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Table 3 *Comparison between phase 1 trial and control groups*

	Trial group (n = 200)	Control group (n = 200)
Age (years)*	31·9	33·6
Hospital stay (days)*		
Preoperative	1·8	3·9
Postoperative	1·9	7·4
No. of wound infections	8	7
Overall complication rate (%)	8·5	5·5

*Values are means

Table 4 *Comparison between phase 2 trial and control groups*

	Trial group (n = 186)	Control group (n = 180)
Age (years)*	37·3	38·9
Hospital stay (days)*		
Preoperative	3·9	3·6
Postoperative	4·1	8·9
Complication rate (%)		
Infection	1·1	3·8
Transient fever	6·4	3·8
Local collection	2·7	3·8
Wound discharge	2·2	2·5
Flap necrosis	2·7	2·5
Miscellaneous	4·8	6·3
Total	19·9	22·8

*Values are means

until the next operating day. The mean preoperative hospital stay was 1·8 days. Patients were discharged as soon as possible, varying from the evening of the day of operation to 4 days after surgery. The mean postoperative stay in hospital was 1·9 days and the mean total hospital stay therefore 3·7 days. Complications occurred in 17 patients (8·5 per cent): eight had wound infection, two drug rash, two transient fever and five miscellaneous problems. No patient with a complication was discharged and none required readmission. There were no deaths.

All patients attended the first follow-up visit. The mean number of hospital visits per patient was 1·6 (range 1–7), the highest number being in a patient who developed wound infection. The questionnaire revealed that 185 patients (92·5 per cent) approved of short-stay surgery; 12 (6·0 per cent) were dissatisfied and three (1·5 per cent) could not be properly assessed. Of patients' families, 66·5 per cent were satisfied with short-stay surgery; 10·0 per cent were not and 23·0 per cent were unavailable for questioning. Of patients with complications, 29 per cent were dissatisfied compared with 4 per cent of those without ($P < 0·001$, z test). The duration of hospital stay did not relate significantly to patient satisfaction.

In comparison, the mean duration of stay of the control patients was 3·9 days before and 7·4 days after surgery, a mean total of 11·3 days. Thus a mean of 7·6 bed-days was saved for each study patient, or 1520 bed-days for the entire group. The complication rate among control patients was 5·5 per cent, with seven having wound infection. These values are not significantly different from those of the study group (*Table 3*).

Phase 2

The mean preoperative hospital stay of the 186 study patients was 3·9 days. The factor most commonly delaying surgery and prolonging hospital stay was lack of operating time (33 patients). Other important causes were late radiology appointments (nine patients) and associated medical problems that required assessment and treatment on an inpatient basis (12). The mean postoperative stay was 4·1 (range 2–7) days, giving a mean total stay of 8·0 days. The complication rate was 19·9 per cent, including 4·8 per cent that occurred after discharge. Most complications were minor wound collections, non-specific short fevers and stitch sinuses (*Table 4*). One patient who had significant flap necrosis after radical mastectomy and a second who developed adhesive intestinal obstruction after hemicolectomy required readmission. The readmission rate was thus 1·1 per cent.

Table 5 *Summary of results*

No. of patients	386
Age (years)*	34·5
Total hospital stay per patient (days)*	5·8
Net bed-days saved	2357
Patient satisfaction (%)	95·6
Morbidity rate (%)	9·6
Mortality rate (%)	0
Readmission rate (%)	0·5

*Values are means

Follow-up was complete at 1 month, with a mean of 2·3 postoperative hospital visits per patient. Of the patients, 182 (97·8 per cent) approved of short-stay surgery, as did 181 families (97·3). The following factors led to dissatisfaction: inadequate analgesic prescription (three patients and their families), domestic problems (one patient and family) and the occurrence of fever at home (one family). Otherwise the occurrence of complications did not lead to dissatisfaction among patients or families.

In the control group the mean total hospital stay was 12·5 days (3·6 days before surgery, 8·9 days afterwards) and the complication rate 22·8 per cent ($P > 0·05$). There was a mean saving, therefore, of 4·5 bed-days for each of the 186 patients, amounting to 837 bed-days saved for the group, which represented 37·2 per cent of all patients undergoing major surgery in the unit during the period of this phase of the study.

The combined results of both phases of this study are summarized in *Table 5*. Overall, 95·6 per cent of patients were satisfied with early discharge. The complication rate of 9·6 per cent was not significantly different from that of the controls (13·4 per cent). A total of 2357 bed-days were saved during the study.

Discussion

The concept of home convalescence after operation is not new; starting with Nicoll[9] in 1909, there have been a succession of reports on the subject[5,10–13]. These studies dealt mainly with what would now be called minor and intermediate operations, such as hernia repair and stripping of varicose veins. By the 1960s, ambulatory surgery had become accepted for a large number of conditions and up to 40 per cent of all procedures have now been described as suitable for outpatient or day-care surgery[14]. Early discharge of suitably selected patients does not increase complication rates[15]. It has been pointed out that morbidity begins in the operating room, not at home[16], and clinicians may tend to be meticulous with a patient scheduled for early discharge to minimize complications. Patient care standards should, if anything, be improved by a policy of early discharge.

Isolated studies have shown success with major procedures performed on an outpatient or ambulatory basis, such as thyroidectomy[17], mastectomy[2,18] and cholecystectomy[19–22]. Most surgeons would not go so far, but the past few years have witnessed a trend towards diminishing hospital stay following major surgery in both Europe and North America. The mean duration of stay for cholecystectomy in hospitals in England and Wales varied from 9·8 to 10·8 days in 1981; the values for 1986 were 8·4–8·9 days[23]. Similar trends have been noted for many other operations. While turnover in operations performed in England and Wales increased by 39 per cent between 1948 and 1964, there was only a 1 per cent concomitant increase in bed numbers[5].

The two most important factors encouraging such changes have been shortage of hospital beds, resulting in long waiting lists, and economic considerations. About half the cost of inpatient care is related directly to hospital stay[1,2] and, with the diagnostic related group-based prospective payment system in the USA, prolonged hospital stay has become non-remunerative. Reimbursement organizations in the USA encourage their clients to avail themselves of cheaper healthcare options such as ambulatory surgery as far as possible. One North American study estimated that national savings would approach US$ 800 million if 30 per cent of all surgical procedures, instead of the then current 10 per cent, were performed on an ambulatory basis[24].

Success with short stay has been reported in almost all fields, including ophthalmic surgery[1,25,26], paediatric surgery[27], gynaecology[1,24,28,29], orthopaedics[23], otolaryngology[1,30,31], plastic surgery[1,32] and neurosurgery[33]. The age of the patient is no longer an important consideration in assessing suitability for short-stay surgery; in the USA even the elderly will not now be reimbursed for admission to hospital after hernia repair[15]. Similarly, the presence of systemic disease, including heart disease and diabetes mellitus, is no longer a contra-indication to early discharge[34]. For a patient whose only requirement is limited nursing care, prolonged hospitalization is a waste of the time and skills of highly trained personnel.

In India, as in developing countries generally, financial considerations are particularly relevant. The country can ill afford the financial burden even of the inadequate number of beds presently available, and more beds are needed to meet the requirements of the rapidly growing population. It is important, then, to consider the advantages of short-stay surgery, but certain disadvantages must not be forgotten. First, the proportion of more seriously ill patients in hospital increases, which strains hospital resources and imposes an additional burden on hospital personnel[21]. Second, the patient is given less time to adjust to new surroundings. Third, an additional workload is thrust on general practitioners, visiting nurses and outpatient staff[6–8]. Finally, home care increases the number of follow-up visits that the patient makes to hospital, and so increases the patient's costs[35].

In general, patients approve of short-stay surgery. Financial considerations apart, there is emotional support to be derived from the family. Also, the patient's confidence increases with early discharge, and disrupted routines are re-established more quickly. With the local problem of beds in part solved, we are now faced with a lack of theatre time for routine operations. This remains the single most important factor prolonging the hospital stay of those undergoing elective surgery. As a consequence, patients awaiting elective procedures may not profit significantly from the beds created by a policy of early discharge.

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Bile duct injury and bile leakage in laparoscopic cholecystectomy

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Between January 1991 and July 1992, 350 laparoscopic cholecystectomies were performed. There were six biliary complications (1·7 per cent): common bile duct (CBD) injury (one patient), delayed CBD necrosis (one), immediate postoperative bile leakage (one) and delayed bile leakage (three). All six patients required laparotomy. Primary repair with long-arm T tube splinting for 3 months was performed for the CBD injury. Religation of the cystic duct was carried out after immediate postoperative bile leakage. Laparotomy with T tube choledochostomy only was performed in the three patients with delayed bile leakage, and hepatojejunostomy Roux-en-Y was undertaken for CBD necrosis. The patient with primary repair of the CBD injury required choledochojejunostomy Roux-en-Y 18 months later for stenosis. Episodes of intermittent cholangitis occurred in the patient with CBD necrosis. The outcome for the four patients with bile leakage was good. There were no deaths.

Since 1987, laparoscopic cholecystectomy has gained wide acceptance and enthusiasm throughout the world[1–4], because of the apparent reduction in postoperative pain and incidence of respiratory complications, shorter hospital stay, reduced recuperation time and possibly lower medical costs[5–7]. However, the incidence of common bile duct (CBD) injury in laparoscopic cholecystectomy (0·33–2 per cent)[8–10] is higher than that of the open operation (0·2 per cent)[11–13]. Among the first 350 laparoscopic cholecystectomies performed in this unit from January 1991, six biliary complications were encountered: two bile duct injuries and four instances of bile leakage. The purpose of the present study was to evaluate these cases retrospectively so as to avoid such complications in the future.

Patients and methods

Between January 1991 and July 1992, 350 laparoscopic cholecystectomies were performed by ten surgeons independently, following the general principles described by Zucker *et al.*[4] with only minor modifications. Briefly, the dissection was begun by releasing the lateral attachment of the gallbladder to the liver. Identification of the cystic duct–CBD junction was not routinely performed. Dissection in Calot's triangle was kept close to the gallbladder to avoid excessive dissection over the major bile duct. Conversion to laparotomy was required in 12 cases. Major complications arose in nine cases (2·6 per cent): subhepatic abscess (three patients), bile duct injury (two) and bile leakage (four). The biliary complications were encountered by three different surgeons.

The charts and available videotapes of the six cases of biliary complication were reviewed retrospectively. The number of previous laparoscopic cholecystectomies performed by the surgeon at the time of complication, the causes of the complications and the management and outcome were thoroughly recorded and followed. Details of biliary anatomy, sites of biliary injury or leakage and possible mechanisms were reconstructed diagrammatically.

Results

The six patients comprised four men and two women of mean age 56·2 (range 35–70) years. All six had symptomatic gallstones diagnosed by abdominal ultrasonography. Results of preoperative liver function tests were within normal limits.

The findings are summarized in *Table 1*. Bile duct injury and early bile leakage occurred in the early learning phase of the surgeon, all within the first five procedures. Delayed bile leakage occurred in the 'maturing' phase of the surgeon.

The sites of bile duct injury and bile leakage are shown in *Figure 1*.

In patient 1, axial traction on the infundibulum allowed the CBD to be mistaken for part of the cystic duct. Injury to the CBD was recognized immediately and primary repair performed after conversion to an open procedure.

In patient 5, the operation was tedious with a total time of 3 h. Excessive use of electrocautery was revealed on review of the videotape. At laparotomy on day 10 after laparoscopic cholecystectomy nearly the whole length of the extrahepatic bile duct was necrotic.

Immediate postoperative bile leakage in patient 4 was caused by an accidental cut to the cystic duct proximal to the clip during dissection of the adjacent cystic artery. The injury was not recognized during operation, although transient bile leakage was noted. Religaton of the cystic duct near the CBD was performed at laparotomy on the second day after operation.

Delayed bile leakage after laparoscopic cholecystectomy was

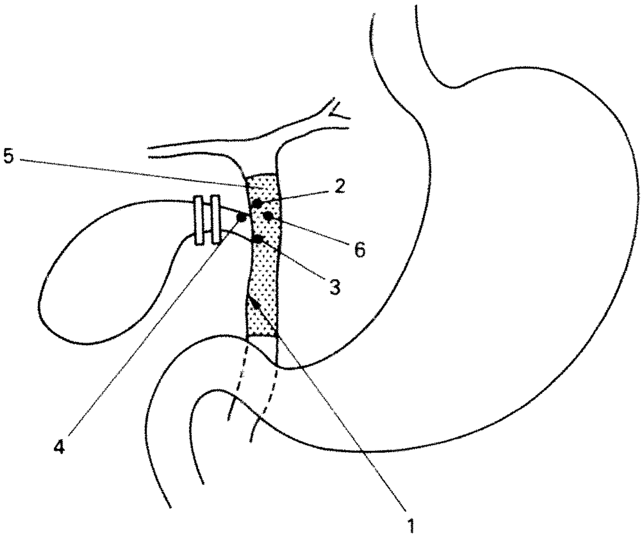

Figure 1 *Sites of bile duct injury and bile leakage in six biliary complications of laparoscopic cholecystectomy. The perforation sites of delayed bile leakage in patients 2, 3 and 6 were within 0·5 cm of the cystic duct–common bile duct (CBD) junction. Numbers relate to the patient numbers in* Table 1. ▨, *CBD necrosis in patient 5*

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Table 1 *Bile duct injury and bile leakage in laparoscopic cholecystectomy*

			No. of laparoscopic cholecystectomies at time of injury							
Patient no.	Sex	Age (years)	Surgeon	Hospital	Complication	Mechanism	Day of occurrence	Risk factor	Management	Outcome
1	F	70	5	5	CBD injury	Short cystic duct, axial traction, failed operative cholangiography	0	Inexperience of surgeon	Primary repair with T tube splinting	CBD stricture 18 months later
2	M	65	39	39	Delayed bile leakage	Delayed electrocautery injury of cystic duct–CBD junction	12	Smoky abdomen	Laparotomy, T tube insertion	Good; T tube removed 30 days later
3	M	48	89	100	Delayed bile leakage	Delayed electrocautery injury or pigtail erosion	13	Smoky abdomen, pigtail erosion	Laparotomy, T tube insertion	Good; T tube removed 7 days later
4	M	35	3	113	Early bile leakage	Injury of cystic duct near CBD junction	2	Inexperience of surgeon	Laparotomy, religation of cystic duct	Good
5	F	63	3	119	Delayed CBD necrosis	Delayed electrocautery injury	10	Inexperience of surgeon, low placement of subxyphoid trocar	Laparotomy, hepatojejunostomy Roux-en-Y	Intermittent cholangitis
6	M	56	110	160	Delayed bile leakage	Delayed electrocautery injury of cystic duct–CBD junction	14	Smoky abdomen	Laparotomy, T tube insertion	Good; T tube removed 12 days later

CBD, common bile duct

caused by delayed electrocautery injury in patients 2, 3 and 6. In these cases, dissection at Calot's triangle was tedious and difficult in a smoky abdomen. In two cases, a drain was left in Morrison's pouch. This was removed 48 h later and demonstrated the absence of early bile leakage. These two patients experienced sudden onset of right upper quadrant pain 8–9 days after operation and were taken to the emergency room on the 12th–14th day after surgery. In patient 3, a right subhepatic abscess necessitated percutaneous catheter drainage on day 8 after operation. Bile leakage was absent at that time and did not appear in the drainage tube until the 12th day after surgery. Exploratory laparotomy revealed a CBD perforation within 0·5 cm of the cystic duct–CBD junction. All appeared to be the result of coagulation necrosis. The cystic stump and clips were intact. T tube choledochostomy with adequate drainage was performed in all three cases.

All six patients were followed for 4–22 months, up to November 1992. They were all well except patient 5, who required oral antibiotic treatment for the control of intermittent subclinical cholangitis.

Discussion

Biliary complications during and after laparoscopic cholecystectomy include bile duct injury and bile leakage. They remain the most critical drawbacks of laparoscopic compared with open cholecystectomy[2–10]. It should be the aim of all laparoscopic surgeons to reduce the incidence of bile duct injury[11–14]. Hunter[14] has proposed five steps that should be followed to avoid this type of injury during laparoscopic cholecystectomy.

Major bile duct injury tends to occur within the first ten to 15 operations performed by a laparoscopic surgeon[4,6], as demonstrated by patients 1 and 5 in the present series. Cutting or transection of the major bile duct can take place if the major duct is mistaken for the cystic duct, as in patient 1, which was only the fifth operation performed by the surgeon. Ways to avoid this kind of complication include: (1) avoidance of axial traction on the infundibulum, as this brings the cystic duct parallel to the CBD; (2) identification of the infundibulum–cystic duct junction before division of the cystic duct, even if this means tedious stripping of much areolar tissue; (3) routine performance of intraoperative fluoroscopic cystic duct cholangiography; and (4) assistance from an experienced laparoscopic surgeon for the first ten to 15 procedures.

Excessive electrocautery can cause delayed CBD injury. The potential hazard inherent to this energy source was pointed out by Moossa *et al.*[15]. Delayed necrosis of the extrahepatic bile duct caused by electrocautery injury, as in patient 5, has not been previously reported[15,16]. This complication is avoidable by conversion to open operation rather than persisting with a difficult and tedious procedure.

Although review of the videotapes of patients 2, 3 and 6 did not identify a direct electrocautery injury, the coagulative nature of the pinhole perforation, intact cystic stump and clips found at reoperation suggested that the injury was caused by electrocauterization. Two possible reasons for these delayed electrocautery injuries are: (1) inadvertent electrocauterization of areolar tissue overlying the CBD or common hepatic duct during dissection of the medial aspect of the cystic duct; and (2) 'cross-fire' electrocautery injury from a dissector through the infundibulum grasper down to the cystic duct–CBD junction during dissection of the lateral side of the cystic duct. Suggested methods of preventing delayed bile leakage are: (1) avoid excessive or tedious dissection over the common hepatic duct or CBD, keeping the dissection as close to the gallbladder as possible; (2) during dissection on the lateral side of the cystic duct, avoid contact between the dissector and the cystic duct or infundibulum grasper – grasp the areolar tissue and electrocauterize away from the cystic duct; and (3) use the smoke evacuator to minimize the amount of smoke within the abdomen and keep the visual field clear.

Although several authors[17,18] have reported open surgery to be the procedure of choice in the management of biliary complications following cholecystectomy, percutaneous catheter drainage without biliary stenting is advocated for bile leakage from the accessory duct or duct of Luschka by Dubois *et al.*[1] and Peters and colleagues[9]. Percutaneous drainage of bile leakage with endoscopic biliary stenting are advocated and usually suffice for simple leakage from small perforations in the major bile duct or cystic duct fistula[19,20]. However, emergency laparotomy is necessary when endoscopic biliary stenting fails, as in patient 3, or when delayed bile leakage presents as biliary peritonitis, as in patients 2 and 6.

Immediate operative management of major bile duct injury during and after laparoscopic cholecystectomy includes primary repair or anastomosis of the clean-cut bile duct injury[21], as in patient 1, or hepatojejunostomy Roux-en-Y for CBD necrosis, as in patient 5 and for the classical transection of the CBD that is unrecognized at the time of operation as proposed by Davidoff *et al.*[16].

If the major bile duct injury is recognized in the immediate postoperative period, presenting as bile leakage, fistula or peritonitis, external biliary drainage is the best initial approach to bring local and systemic septic conditions under control. If the bile duct injury presents at an interval after laparoscopic cholecystectomy and the local condition is acceptable, as in patient 5, single-stage repair with a Roux-en-Y jejunal loop may be achieved. The prognosis of patients with major bile duct injury is usually poor, whereas that after bile leakage is uniformly good. The present results confirm this.

Biliary complications occurring during or after laparoscopic cholecystectomy include major bile duct injury and bile leakage. The former usually occurs in the early learning phase of the surgeon. Abiding by Hunter's rules for avoiding bile duct injury, assistance from an experienced laparoscopic surgeon for the first 15 procedures and a liberal policy towards conversion to open cholecystectomy when in doubt are likely to reduce the incidence of duct injury. Avoidance of excessive electrocautery and clear visualization are the best means of preventing delayed bile leakage.

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Preventing complications of laparoscopy

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Laparoscopy was first performed by Kelling[1] in 1901, but it was not until the 1950s in Europe and the late 1960s in the USA that the technique gained popularity. The past 4 years has seen an explosion in the use of laparoscopic techniques in general surgery. Closed laparoscopy, using a Veress needle for insufflation followed by blind insertion of a sharp trocar and cannula, has been the predominant method of gaining access. The open technique, which is performed by making a small subumbilical laparotomy incision under direct vision and inserting a blunt Hasson's trocar and cannula (with a cone to prevent air leakage), has been reserved mainly for patients with adhesions from previous abdominal surgery.

The most catastrophic and feared complication of laparoscopy is injury to the major retroperitoneal vessels. In gynaecological series the incidence of this disaster is between 3 and 10 per 10000 closed laparoscopies[2–4]. Although the development of disposable trocars with spring-loaded safety shields and improvements in technique may have reduced the risk of this potentially fatal complication, reports from general surgery indicate that they do not prevent it[5–7]. One reason for this is that the external safety shield of the trocar is often held back by a loose layer of peritoneum after it has entered the abdomen, leaving the sharp trocar exposed[5]. In a survey throughout the United States[7], 36 major retroperitoneal vessel injuries – three of which resulted in death – were reported in a series of 77604 laparoscopic cholecystectomies, an incidence of nearly 5 per 10000. These injuries were attributed mainly to trocar insertion. On the other hand, the 35 injuries to other intra-abdominal vessels (incidence 5 per 10000) were attributed mainly to insertion of the Veress needle. Vascular injury at the time of insertion of additional trocars should never occur, as these can be introduced under direct laparoscopic vision. Major vascular injury can be completely eliminated by routine use of open laparoscopy. Penfield[8] reported no vascular injuries in almost 11000 such operations performed by 18 gynaecologists in the United States.

Another serious complication of closed laparoscopy is hollow viscus perforation[4]. Perforation of the small bowel, colon, stomach, bladder, uterus and ureter have all been reported. In the American survey of laparoscopic cholecystectomy previously mentioned[7], 109 bowel injuries (five fatal) were reported, an incidence of 0·14 per cent; this figure is identical with the incidence found in gynaecological experience[9]. These injuries, which are typically unrecognized at the time of operation, often present late with peritonitis, intra-abdominal abscess or enterocutaneous fistula[7], and they may result in death[10]. Although bowel laceration can occur with open laparoscopy (6 in 11000), the major advantage of this method is that accidental perforation is usually recognized and can be repaired at the time of operation (four of six)[8].

Complications related to pneumoperitoneum are gas embolus, cardiovascular collapse, pneumothorax and hypercarbia caused by carbon dioxide absorption. Gas embolus is exceedingly rare, occurring in fewer than 1 in 10000 procedures[11–13]. It is usually secondary to accidental intravascular injection of carbon dioxide during insufflation through a misplaced Veress needle, but it has also been reported as a result of accidental placement of an air-cooled laser tip into a vessel[14]. Embolization to the right ventricle and pulmonary circulation may be delayed by up to 1 h by passage through the portal system[15]. An early sign of air embolism is a sudden fall in end-tidal carbon dioxide[14,16]. When air embolism is suspected, the abdomen should be deflated, the patient tilted head-down and positioned on the left side[17], and nitrous oxide anaesthesia discontinued[18]. A central line should be inserted into the right ventricle for aspiration of gas bubbles[19]. The most sensitive method of identifying air embolism is Doppler ultrasonography, which can detect as little as 0·1 ml air in the right ventricle[20]. Cardiovascular collapse may occur as a result of a profound vasovagal response to rapid peritoneal distension[21]. Tension pneumothorax is usually the result of a congenital defect of the diaphragm (a patent pleuroperitoneal canal)[22], although accidental perforation of the diaphragm by a gallbladder-retracting forceps is another cause[23].

During prolonged laparoscopic procedures, absorption of carbon dioxide may result in significant hypercarbia and acidosis[24,25]. Therefore, careful monitoring of carbon dioxide tension and an increase in ventilation minute volume is required. Measurement of end-tidal carbon dioxide levels gives some indication of the arterial partial pressure, but arterial carbon dioxide tension may range between 2 kPa above and 1 kPa below the end-tidal value[25]. In patients with severe respiratory disease, the rise in arterial carbon dioxide level may be particularly marked[26]. The use of helium instead of carbon dioxide may resolve this problem[25,27,28].

Other major complications encountered during laparoscopic surgery include thermal injury to the abdominal wall, bowel and common bile duct[29–31]. These injuries can occur with the use of either monopolar electrocautery[31,32] or laser[30] and often result from a poor understanding of the basic concepts of these energy forms[33,34]. Another avoidable complication of both open and closed laparoscopy is herniation of bowel through the trocar insertion site[35,36]. This occurrence is more likely when the site is enlarged to remove, for example, the gallbladder at laparoscopic cholecystectomy. Suture closure of the fascial defect is therefore required.

Surgeons have favoured closed laparoscopy because it is thought to be faster and less cumbersome than the open method. This is a misconception; open laparoscopy should have a shorter and safer learning curve for general surgeons in training. Moreover, it also removes the need for urinary catheterization and allows faster insufflation. Finally, open laparoscopy should result in significant cost savings over the closed method in which a disposable Veress needle and trocar are used, as the argument for always having a sharp new instrument does not apply.

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Subumbilical hernia following laparoscopic cholecystectomy

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Laparoscopic cholecystectomy has been routine in the authors' unit since 1990. Practice has been to remove the excised gallbladder through the subumbilical trocar site. This fascial incision is made with a 10-mm trocar and cannula, and accommodates the laparoscope throughout the operation. The fascial defect is routinely closed with a non-absorbable suture when enlargement or dilatation is necessary to remove the gallbladder. To date, however, it has not been practice to close this defect after uncomplicated delivery of the gallbladder from the peritoneal cavity. Unexpected development of a subumbilical hernia is reported in two patients following uncomplicated laparoscopic cholecystectomy.

Case reports

Patient 1

A 71-year-old woman with mixed cardiac valvular disease receiving oral anticoagulation therapy presented with biliary colic. Ultrasonography showed multiple gallstones in a thickened gallbladder. The woman had a previous history of intermittent attacks of biliary colic and had been turned down for elective surgery because of anaesthetic risk. She was scheduled for laparoscopic cholecystectomy.

The operation was uneventful and the mobilized gallbladder was easily delivered. The patient remained in hospital while oral anticoagulation was re-established. On day 5 after operation the skin sutures were removed from the subumbilical incision. Approximately 2 h later, three loops of small bowel prolapsed through the subumbilical stab wound. Under local anaesthesia the skin and fascia were incised and the intestine reduced. Nylon sutures were then placed in the fascia and skin. The patient made an uneventful recovery.

Patient 2

A 70-year-old woman presented with a tender central abdominal swelling 18 months after uneventful laparoscopic cholecystectomy. A diagnosis of subumbilical incisional hernia was confirmed at elective operation the following day. The omentum had prolapsed through a 12-mm defect (*Figure 1*); this was enlarged and the omentum reduced. The fascia was then repaired with non-absorbable sutures. The patient was well on discharge the next day.

Discussion

Herniation through the abdominal wall is recognized by gynaecologists as a complication of laparoscopy. However, general surgeons are less aware of the problem. Sauer and Jarrett[1] reported small bowel obstruction after laparoscopy and, while acknowledging that herniation was a rare event, warned that small bowel incarceration in a subumbilical wound should be considered in a patient presenting with relevant signs, irrespective of the intervening time period. Others have noted the development of an incarcerated hernia following laparoscopy[2] and laparoscopic sterilization[3].

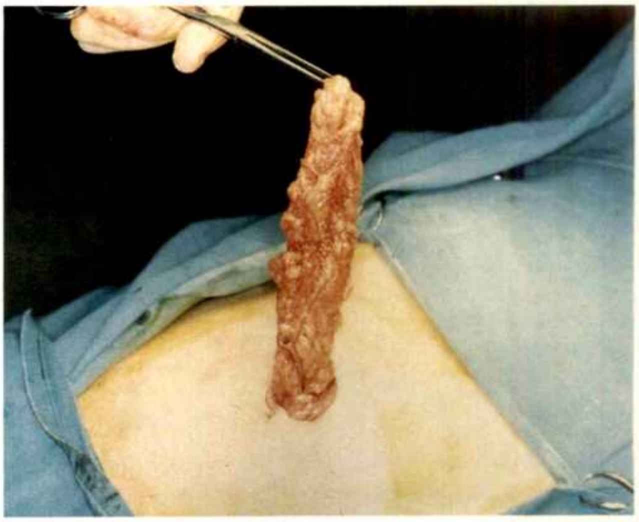

Figure 1 *Patient 2: herniation of omentum via the subumbilical port in a 70-year-old woman following routine laparoscopic cholecystectomy*

Maio and Ruchman[4] reported a case of incisional hernia following laparoscopy that was diagnosed by computed tomography. Such an expensive investigation is neither necessary nor justified in the detection of this complication, except perhaps in a very obese patient. Some authors[5] have suggested that the centre of the umbilicus should be the entry site for the laparoscope, but there is no evidence that this approach prevents incisional hernia.

It is easy to understand why herniation could follow laparoscopy when the subumbilical incision site has been enlarged or stretched to remove the mobilized gallbladder. However, epigastric and femoral hernias commonly occur through fascial defects no larger than those resulting from insertion of 5- or 10-mm trocars. Distension of the abdominal musculature during laparoscopy may contribute to postoperative herniation.

Many surgeons currently remove the gallbladder via the epigastric port; intervening muscle layers between the peritoneal cavity and skin may be less amenable to herniation. This practice may well reduce the incidence of this complication, but only anecdotal evidence supports this theory at present.

We are sufficiently concerned at this stage to recommend routine closure of the subumbilical fascial defect after laparoscopic surgery.

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Surgical management of perineal and metastatic cutaneous Crohn's disease

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Skin lesions are the commonest extraintestinal manifestation of Crohn's disease. Lesions that develop at sites remote from the gastrointestinal tract and have granulomas on histological examination are termed metastatic cutaneous Crohn's disease. Management is difficult as medical treatment is often ineffective. This report describes the use of surgical debridement of areas of perineal metastatic cutaneous Crohn's disease in five patients, all of whom had failed to improve after a variety of medical treatments. One patient had a poor result with continuing mild perineal discharge and four had a good outcome with complete resolution of symptoms and satisfactory cosmetic results.

Crohn's disease is a granulomatous inflammatory condition that can affect any part of the gastrointestinal tract. A variety of extraintestinal manifestations are recognized[1], the most frequent being cutaneous involvement. Dermatological complications occur in up to 44 per cent of patients with Crohn's disease[2]. Patients may develop granulomatous inflammation of the skin at sites remote from the gastrointestinal tract: metastatic Crohn's disease[3] or more commonly metastatic cutaneous Crohn's disease[4,5]. Management of cutaneous lesions continues to present a therapeutic challenge. A variety of agents have been reported to be beneficial but no clear-cut therapeutic regimen exists. This report describes five patients with cutaneous Crohn's disease treated by wide local excision of the affected areas after failed medical management.

Case reports

Patient 1

A 25-year-old man underwent panproctocolectomy and formation of a Brooke ileostomy in 1986. He developed increasing discharge from the perineum and the sinuses present were laid open, with minor symptomatic improvement. Skin biopsy revealed the presence of non-caseating granulomas consistent with a diagnosis of Crohn's disease. Prednisolone, azathioprine, dapsone, antibiotics and hyperbaric oxygen failed to control the disease, which extended to the lower lumbar region and both groins, causing penile oedema. In March 1991 the patient underwent extensive debridement of the affected area. Diseased tissue was excised down to deep fascia and the wound was left to heal by secondary intention. After 1 year the wounds healed, the penile oedema subsided and there remained a few sinuses in the area that had not been excised.

Patient 2

A 50-year-old man was referred with a 3–4-year history of chronic discharging sinuses of the perineum and right thigh, and penile oedema. Rectal sinography confirmed a fistula connecting the rectal stump and a right-sided pelvic cavity. Proctectomy did not resolve the problem and perineal sepsis continued (*Figure 1a*). Some 6 months later the patient underwent extensive debridement of the affected skin around the scrotum, perineum and right buttock. A meshed split-skin graft was applied to the defect 48 h later. Histological examination revealed non-caseating granulomas and other features consistent with cutaneous Crohn's disease. The wounds remain healed with no sepsis 16 months later (*Figure 1b*).

Patient 3

A 54-year-old man had had a chronic discharging perineal sinus since 1960. This progressed to the surrounding skin, and in 1986 and 1987 the areas involved were conservatively debrided. Histological analysis confirmed cutaneous Crohn's disease. The man continued to have marked perianal and gluteal sepsis. Azathioprine produced some initial resolution but another gluteal abscess developed. Cyclosporin and subsequently prednisolone failed to control the perianal disease and in September 1990 the patient underwent debridement and split-skin grafting of the affected gluteal skin. After 10 months there is minimal discharge from the perineum.

Patient 4

A 48-year-old diabetic woman was referred with a 5-year history of a chronically discharging 'rash' of the groin and perineum. She had undergone panproctocolectomy and ileostomy for Crohn's disease in 1973. Skin biopsy confirmed the presence of non-caseating granulomas and appearances consistent with a diagnosis of Crohn's disease. Cyclosporin and metronidazole produced limited initial improvement. In November 1991 the patient underwent excision of the affected skin and subcutaneous tissue in the perineum and groin, down to the deep fascia. The defect was allowed to granulate and by 12 months the wounds were completely healed.

Patient 5

A 23-year-old woman was referred in 1985 with severe perianal Crohn's disease. Following subtotal colectomy and ileostomy she developed persistent perianal and vulval discharge. This continued despite medical treatment with steroids, azathioprine, prolonged metronidazole and mercaptopurine. Skin biopsy had demonstrated active, severe, chronic inflammation associated with many non-caseating granulomas, consistent with cutaneous Crohn's disease. In January 1992 the perineal disease worsened. Examination under anaesthesia revealed marked perineal and vulval cutaneous disease with radial ulceration (*Figure 2a*). The patient underwent wide excision of the affected perineum and approximately two-thirds of the vagina circumferentially, leaving the cervix and a longer anterior than posterior vaginal wall. The perineum and vagina was reconstructed with a gracilis myocutaneous and a posterior thigh fasciocutaneous flap (*Figure 2b*). The cosmetic and functional results have been more than satisfactory at 6-month follow-up.

The chronological sequence of disease progression and surgical intervention in the five patients is shown in *Table 1*.

Table 1 *Chronological summary of events*

	Patient no.				
	1	2	3	4	5
Sex	M	M	M	F	F
Age (years)	30	50	54	50	30
Age at disease onset (years)	19	26	22	31	9
Age at bowel resection (years)	20	30	24	34	12
Age at proctectomy (years)	25	49	25	34*	12·5*
Duration of symptoms after proctectomy (years)	5	0·4	25	5	18
Colonic disease	Yes	Yes	Yes	Yes	Yes

*Proctectomy performed as a separate procedure

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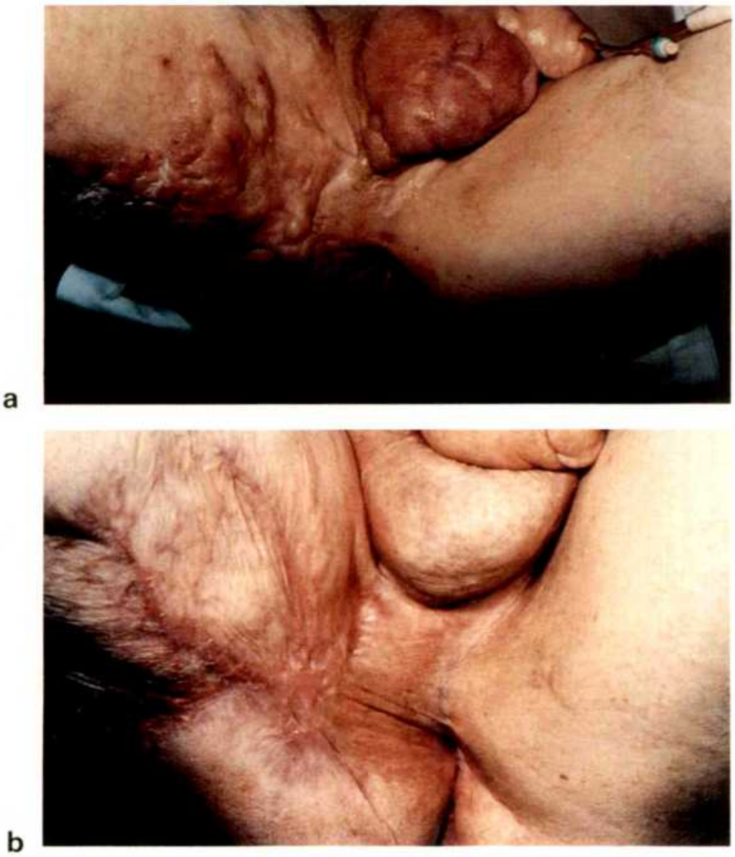

Figure 1 *Patient 2.* **a** *Preoperative appearance with involvement of the perineum and posterior thigh.* **b** *Appearance at 16 months*

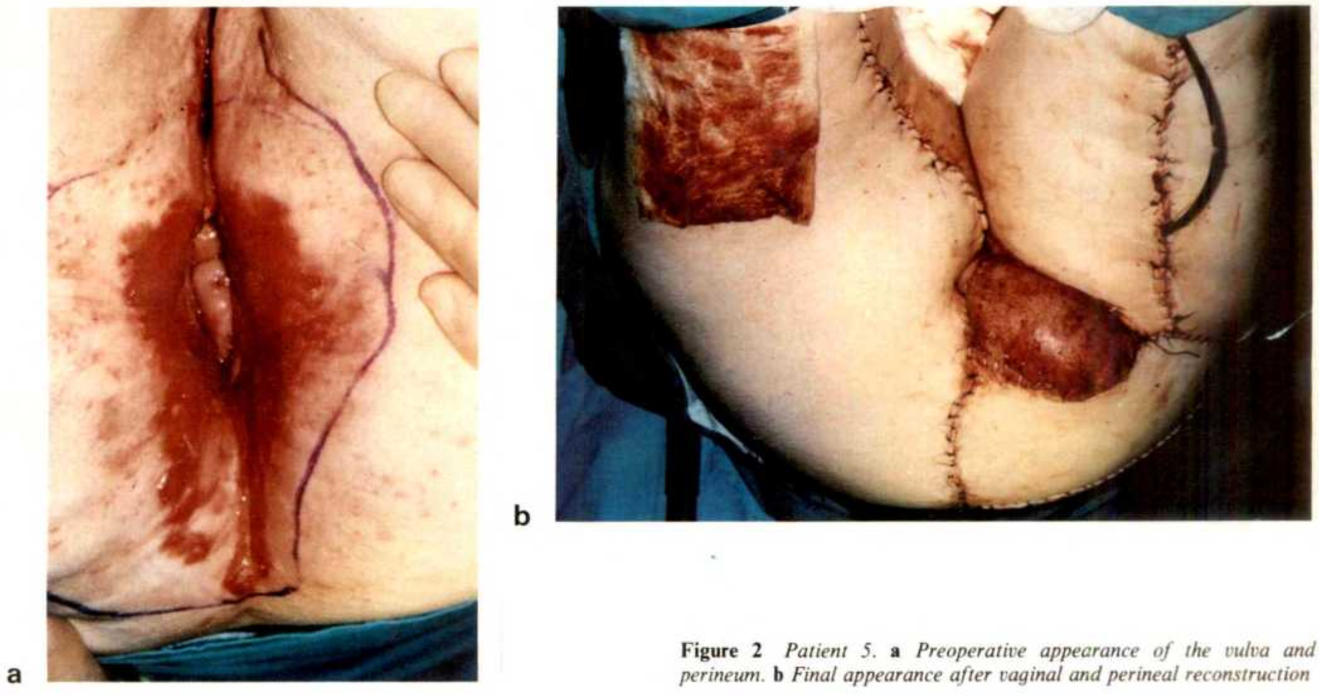

Figure 2 *Patient 5.* **a** *Preoperative appearance of the vulva and perineum.* **b** *Final appearance after vaginal and perineal reconstruction*

Discussion

Metastatic cutaneous Crohn's disease is histologically similar to direct contiguous cutaneous disease but occurs at sites remote from the gastrointestinal tract and appears as ulcers in flexural[2] and non-flexural[6,7] sites and as nodular lesions on the extremities[4,8]. Metastatic lesions are associated with disease that involves the colon; extraintestinal complications of Crohn's disease are more commonly associated with colonic disease[1]. These lesions nearly always follow the onset of gastrointestinal disease. The differential diagnosis of cutaneous Crohn's disease includes other causes of granulomatous inflammation such as syphilis, tuberculosis, actinomycosis, sarcoidosis and hidradenitis suppurativa. Histopathological assessment therefore has a particularly important role in diagnosis. The lesions of Crohn's disease are characterized by granulomatous inflammation with giant cells and discrete non-caseating granulomas within the dermis, occasionally extending into the subcutaneous tissue[8,9]. The granulomas are arranged in a perivascular manner with normal vessel walls[8] and sometimes associated with a granulomatous perivasculitis[10]. The association of Crohn's disease and cutaneous polyarteritis nodosa has been described[11], but it is difficult to ascertain whether the vascular changes are secondary to the granulomatous inflammation or whether they represent a primary vasculitis. The aetiology of Crohn's disease may be vasculitic[12].

The consequences of cutaneous manifestations of Crohn's disease can produce some of the most debilitating complications. There is no consistent relationship between the appearance of the cutaneous lesion and the underlying disease activity of the gastrointestinal tract. Little is known about the natural history of the lesions and empirical treatment is directed at the primary disease process affecting the bowel and local therapy to the cutaneous lesions. The use of immunosuppressive agents[13–15] and metronidazole[3,16] has been associated with good results and hyperbaric oxygen has been reported to be successful in two patients[17,18]. Possible complications of hyperbaric oxygen therapy include middle ear barotrauma, ocular effects, claustrophobia, pulmonary oxygen toxicity and central nervous system oxygen toxicity[17]. Local therapy is predominantly supportive. Intralesional steroids have been used with some success[19,20].

Surgical management has usually included removing bowel affected with Crohn's disease and local procedures such as laying open fistulas, draining of abscesses and local debridement. Surgery has also been used in patients after failed medical management. Surgical treatment was possible in the present group because the disease did not spread below the deep fascia, a feature that has been observed by others[21]. This therefore allows a relatively radical resection of affected tissue down to the deep fascia, which permits healing by secondary intention or skin grafting. Patient 3 had a less than satisfactory result, which was probably caused by an unhealed presacral cavity present at the time of surgical debridement.

Results from this small series of patients demonstrate the utility of surgical debridement in patients with cutaneous Crohn's disease refractory to medical treatment.

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Randomized controlled trial comparing laparoscopic and open appendicectomy

A study was carried out of 137 patients with a diagnosis of acute appendicitis who were randomized to either laparoscopic or open appendicectomy. Patients found to have perforated or normal appendices at histological examination were excluded. Fifty-two patients undergoing laparoscopic appendicectomy and those receiving 57 open procedures were analysed. Laparoscopic appendicectomy took no longer than the open procedure (mean 43 versus *40 min). The number of doses of pethidine (1 mg per kg body-weight) required in the immediate postoperative period did not differ between the two groups but the mean number of doses of oral analgesic (naproxen sodium 550 mg twice daily) required was less in patients undergoing laparoscopic appendicectomy (2·8* versus *5·0,* $P < 0{\cdot}05$*). There was no significant difference between time to resumption of fluid and diet intake and length of hospital stay. There were five (9 per cent) wound infections after open appendicectomy compared with none after the laparoscopic operation (*$P < 0{\cdot}01$*). Patients who underwent laparoscopy returned to full home (17* versus *30 days,* $P < 0{\cdot}01$*) and social (19* versus *32 days,* $P < 0{\cdot}05$*) activities earlier than those who underwent open operation. Laparoscopic appendicectomy may allow reduction in the number of wound infections and earlier return to normal activities.*

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Several series of laparoscopic appendicectomy have been reported in the literature$^{1-4}$, but these are either uncontrolled or non-randomized trials and it remains uncertain whether the laparoscopic approach is superior to the open technique. A randomized trial was conducted to determine whether significant differences occurred between these two procedures with regard to wound infection, duration of the procedure, postoperative analgesic requirement, time to resumption of intake of fluids and diet, hospital stay and return to normal activities.

Patients and methods

Between February and August 1992, all patients over the age of 12 years with a diagnosis of acute appendicitis were randomized to open or laparoscopic appendicectomy. Randomization was achieved with the toss of a coin by independent observers. Seventy-two patients were randomized to open and 65 to laparoscopic operation. Fifteen patients (21 per cent) from the open group were excluded; in 11 the appendix was normal on histological examination and in four it was perforated. Thirteen patients (20 per cent) from the laparoscopy group were excluded; in ten laparoscopy revealed a normal appendix and in three perforation. In patients with a normal appendix, other causes of abdominal pain were found and the appendices were not removed. Patients studied are detailed in *Table 1*. All patients received intravenous gentamicin and metronidazole before surgery. The open technique was performed through a standard right lower quadrant incision, with precautions to avoid unnecessary wound contamination, by registrars or residents with experience of at least 6 months. Of the 52 laparoscopic appendicectomies, 39 were performed by one registrar trained in laparoscopy and the rest by two laparoscopically trained consultants. Only surgeons who had performed more than 15 operations in the respective groups were allowed to participate in the study.

The appendicular artery was secured laparoscopically with Ligaclips (Ethicon, Somerville, New Jersey, USA) before being cut. The base of the appendix was then secured with an Endoloop (Ethicon) and transected. Monopolar diathermy was used sparingly to achieve haemostasis when necessary. Removal of the appendix was achieved through a left suprapubic 10-mm cannula; the wound was not touched in any case. Successful removal of the intact appendix through the cannula was achieved in 43 patients. In nine patients the appendix was too big for the cannula and was placed in the thumb of a size 8 glove and extracted without contamination. There were no conversions to an open procedure. The duration of surgery was defined as the time from skin incision to when the wound was completely dressed.

After the operation, intramuscular pethidine 1 mg/kg every 4 h was given on demand. Oral naproxen sodium (Synflex; Syntex, Auckland, New Zealand) was given as a 550 mg dose twice a day on demand when patients were able to take liquids, and the number of

Table 1 *Results of the randomized controlled trial*

	Appendicectomy		
	Open	Laparoscopic	*P*
No. of patients	57	52	—
Age (years)*	30·7(7·3)	33·1(4·9)	n.s.
Sex ratio (M:F)	0·4:1·0	0·5:1·0	—
Weight (kg)*	57·1(6·2)	57·4(4·3)	n.s.
Duration of operation (min)*	40·1(15·5)	43·4(17·1)	n.s.
Doses of intramuscular pethidine (1 mg/kg)*	1·3(0·3)	1·0(0·3)	n.s.
Doses of oral analgesic (naproxen 550 mg)*	5·0(1·2)	2·8(1·0)	<0·05
Time to resumption of fluid (days)*	1·2(0·4)	0·9(0·2)	n.s.
Time to resumption of diet (days)*	1·8(0·5)	1·8(0·2)	n.s.
Hospital stay (days)*	4·2(1·0)	3·2(0·6)	n.s.
Wound infection†	5 (9)	0 (0)	<0·01
Time to return to full home activities (days)*	30(10)	17(5)	<0·01
Time to return to full social activities (days)*	32(12)	19(6)	<0·05

*Values are mean(s.d.); †values in parentheses are percentages. n.s., Not significant

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doses given recorded. Fluids were prescribed on the return of active bowel sounds; diet was resumed when the patients tolerated fluids well. Patients were discharged when diet was tolerated well and reviewed after 1 week in the outpatient clinic. Wound infection was defined as purulent discharge from the incision site. Patients were interviewed at 1 month to determine the period of debility before returning to full activities. For those who had not returned to full activities by 1 month, a second interview was held 2 weeks later.

Data from the two groups were compared using Student's t test. Proportions were compared with the χ^2 and Fisher's exact tests when necessary. $P < 0{\cdot}05$ was taken as significant.

Results

The two groups were comparable in terms of age, sex and weight (*Table 1*), and most patients were classified as American Society of Anesthesiologists grade I. Diagnosis was confirmed on the finding of transmural infiltration with leucocytes in part or all of the appendix. The lengths of the two procedures were not significantly different and there was no difference in the number of doses of pethidine requested by the two groups. Patients undergoing open operation required more doses of oral analgesic than those receiving laparoscopy (*Table 1*; $P < 0{\cdot}05$). There were no significant differences in the time to return of bowel sounds and commencement of fluids and diet intake, or in the length of hospital stay (*Table 1*). Five patients (9 per cent) had a wound infection after open operation but none after laparoscopy ($P < 0{\cdot}01$). No complications were caused by the laparoscopic technique, and no postoperative abdominal or pelvic abscesses were found in either group.

Patients undergoing laparoscopic appendicectomy incurred a mean of £148 more in charges, which was due entirely to the cost of disposable cannulas and instruments. It was not possible to analyse the delay before return to full work as the wide diversity of occupations between the two groups made the results incomparable. The range of home and social activities were, however, similar in both groups. Return to full activity (ability to pursue activity at a level of intensity, duration and frequency similar to that before operation) took much longer for patients undergoing open appendicectomy ($P < 0{\cdot}01$ for home and $P < 0{\cdot}05$ for social activities) (*Table 1*).

Discussion

Laparoscopy helps avoid misdiagnosis of acute appendicitis[5], but some authors[6] believe that the procedure takes much longer. The results of the present randomized trial show that the total time is comparable if surgeons with similar experience are used for each type of operation. Less oral analgesic was needed by patients undergoing laparoscopy, although the clinical significance of the difference between 5·0 and 2·8 doses is debatable. There was no significant difference in the time to resumption of fluid and diet.

Infection of the wound remains the main cause of postoperative morbidity and prolonged hospitalization in those undergoing open appendicectomy[7]. A reduction in the incidence of wound infection may be an advantage of laparoscopic appendicectomy. Removal of the appendix through the cannula effectively prevents seeding of bacteria in the wound. Patients with perforated appendices were excluded as they represent a subgroup of this condition with a different morbidity and mortality pattern. The difference of 1 day in hospital stay between the two groups, although not statistically significant, was contributed to mainly by the extended hospitalization of up to 12 days in patients with wound infection.

Earlier return to full activity appears to be an important benefit of laparoscopic appendicectomy; a reduction of almost 2 weeks was achieved. Although the cost of the laparoscopic procedure was higher, this could be offset by earlier return to productive activity. There is evidence that postoperative adhesions occur less often with the laparoscopic technique[8]. Adhesion-related complications such as intestinal obstruction and subfertility remain the main source of long-term morbidity from open appendicectomy[9]. The laparoscopic method has the bonus of better cosmesis by placement of the two inferior cannulas below the 'bikini line'.

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Case report

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Colonic obstruction in acute myeloid leukaemia

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Intestinal complications in patients with acute leukaemia are not uncommon; obstructive lesions in the small bowel are the most frequently reported. Intussusception secondary to leukaemic infiltration is thought to be the major precipitating factor in these patients. Large bowel complications are relatively rare: only one case of colonic obstruction has been described previously, in which leukaemic infiltration presented the classical picture of stenosing sigmoid carcinoma[1]. A patient with leukaemia who developed large bowel obstruction requiring surgical intervention is reported.

Case report

A 43-year-old woman with acute myeloid leukaemia presented with haematemesis and melaena during her third course of chemotherapy. At the time she was found to be profoundly depleted of platelets and white cells (haemoglobin level 9·9 g/dl, white cell count $1{\cdot}3 \times 10^9$/l, platelet count 2×10^9/l). Gastroscopy failed to reveal the source of haemorrhage. The patient then proceeded to pass fresh blood rectally and required multiple transfusions of packed red cells and platelets. By 3 days the bleeding had decreased, but the woman started to develop progressive abdominal distension, which was initially thought to be pseudo-obstruction and was treated conservatively. However, the patient developed signs of septicaemia and the abdominal distension progressed. Abdominal radiography revealed right-sided colonic dilatation, which suggested a mechanical obstruction in the proximal transverse colon. To differentiate between mechanical and pseudo-obstruction colonoscopy was performed, but the endoscope failed to advance beyond the descending colon. An urgent barium enema confirmed mechanical obstruction at the site of clinical suspicion. Because of the patient's severe leucopenia and thrombocytopenia surgical intervention was deemed very hazardous and laparotomy seemed inadvisable. Caecostomy was performed to decompress the obstructed colonic segment. The patient's general condition improved rapidly and the bleeding discontinued. Some 2 months later a repeat barium enema revealed a strictured area at the site of the previous obstruction (*Figure 1*). As the patient's haematological parameters had improved (haemoglobin level 10·1 g/dl, white cell count $7{\cdot}1 \times 10^9$/l, platelet count 73×10^9/l), a laparotomy was performed. The proximal transverse colon showed a narrowed thickened area but no signs of continuing obstruction; extended right hemicolectomy was carried out. Histological analysis of the affected segment showed evidence of submucosal thickening, fibrosis and a chronic inflammatory cell infiltrate. However, the inflammatory cells were of normal morphology and there was no evidence of leukaemic cell infiltration. The patient made an uncomplicated recovery and remains well in remission 1 year later.

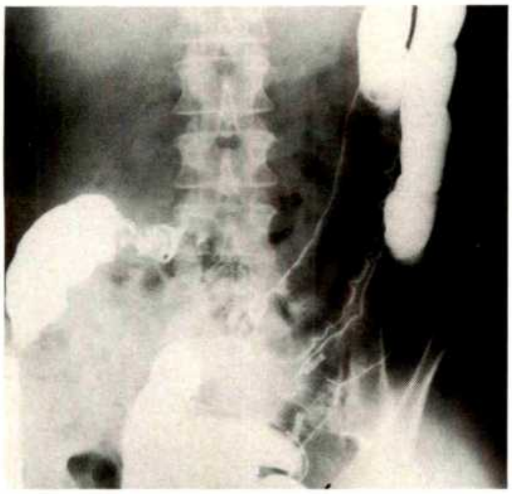

Figure 1 *Contrast enema showing an irregular stricture in the proximal transverse colon*

Discussion

Bleeding, perforation and small bowel obstruction are well recognized gastrointestinal complications in patients with leukaemia. Colorectal complications such as mucosal ulceration, bleeding, caecal perforation, gangrene of the appendix and proctitis have been described[2]. Large bowel obstruction caused by leukaemic infiltration is rare, with only one previous case reported[1]. The present paper describes another case of large bowel obstruction in a patient with acute myeloid leukaemia. Although leukaemic infiltration was not confirmed, only fibrosis of the colonic wall, the fibrosis was thought to be secondary to infiltration that had responded to the chemotherapy administered at the time of presentation of the obstructive episode.

Leukaemic infiltration of the small and large bowel occurs usually as plaque-like thickenings of the submucosa but can manifest as nodular or polypoid lesions[2]. In the small intestine polypoid masses are the most common. Enlargement of these polypoid lesions is thought to predispose to necrosis and subsequent haemorrhage. This complication may occur more commonly in the colon, simulating ulcerative colitis or ileocolitis on microscopic inspection[2]. Previous publications suggest that leukaemic infiltration of the gastrointestinal tract occurs in all types of leukaemia but is less common in the myeloid form[3].

Ischaemia and necrosis of mucosal and submucosal infiltrates has been proposed as the likely cause of pseudo-obstruction, although autonomic dysfunction secondary to a toxic effect of chemotherapy has been implicated. When mechanical obstruction of the small or large bowel has occurred, a nodular leukaemic infiltrate can usually be identified in the submucosa. Luminal occlusion may occur gradually and mimic a malignant lesion, which can be difficult to differentiate on barium enema investigation.

Intestinal obstruction has been well described, especially in acute lymphatic leukaemia. Intussusception is thought to be the mechanism of obstruction in the small intestine[4], the likely cause being a leukaemic infiltration which causes localized thickening of the bowel. In the large bowel, an obstructive lesion or stenosis should always be distinguished from carcinoma.

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Laparoscopic colorectal surgery: a prospective assessment and current perspective

Between August 1991 and June 1993, 74 laparoscopic and laparoscopically assisted colonic and rectal operations were performed. A variety of procedures were carried out including 32 total abdominal colectomies (group 1), 32 segmental resections (group 2) and ten constructions of a diverting stoma without formal resection (group 3). Indications for surgery were mucosal ulcerative colitis in 20 patients, carcinoma in 12, polyposis in six, Crohn's disease in seven and other conditions in the remaining 29. The 74 comprised 42 male and 32 female patients of mean age 45 (range 12–88) years. The median (range) duration of the procedure was 3·0 (1·0–6·5) h for the entire group, 3·9 (2·5–6·5) h for group 1, 2·9 (1·5–5·5) h for group 2 and 1·8 (1·0–2·5) h for group 3. The median (range) length of ileus was 3·0 (2–7) days overall; respective times for groups 1–3 were 3·5 (2–7), 3·0 (2–7) and 2·0 (1–4) days. The median (range) length of hospitalization was 7·0 (2–40) days, 8·1 (4–19) days in group 1, 7·0 (4–20) days in group 2 and 6·0 (2–40) days in group 3. Ten patients (14 per cent) developed intraoperative and 15 (20 per cent) postoperative complications; there were no deaths. These results failed to confirm any significant advantages of laparoscopic or laparoscopically assisted colorectal surgery. Specifically, neither the operating time, nor length of ileus, nor length of hospitalization was improved over standard procedures. Advances in technology and surgical technique may improve such findings in the future.

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Laparoscopic surgery has been successfully used by gynaecologists for more than 15 years[1]. The majority of these procedures were diagnostic, although therapeutic intervention has recently gained widespread acceptance. General surgeons subsequently adopted pelvic laparoscopic techniques for other intra-abdominal applications; cholecystectomy, appendicectomy and herniorrhaphy have become more widely available. Much of the enthusiasm in both the surgical and lay communities has resulted from claims of decreased pain and shorter hospital stay associated with these minimally invasive procedures[2].

In an attempt to introduce these improvements into the field of colorectal surgery, a variety of procedures have been attempted laparoscopically. Anecdotal evidence suggests that some patients who have undergone laparoscopic procedures fared marginally better than historical controls who had similar operations conventionally[3,4]. Other studies have failed to find a clear benefit from the use of laparoscopy in colonic resection[5–7]. The aims of the present study were therefore to assess prospectively the potential value of laparoscopic colorectal surgery. The study analysed morbidity and mortality, and assessed any demonstrable advantages to the patient.

Patients and methods

In February 1991, two members of the Department of Colorectal Surgery (S.D.W., D.G.J.) embarked on a three-phase programme to introduce laparoscopic colorectal surgery to this institution. Phase I consisted of a 6-month period during which extensive experience with laparoscopic bowel resection was gained in animal models. Phase II overlapped with this and included a 3-month period during which skill was developed with laparoscopic cholecystectomy in humans. Phase III, initiated in August 1991, was the performance of laparoscopic colorectal surgery.

In May 1991, in conjunction with the American Society of Colon and Rectal Surgeons, a prospective registry was established[8]. This registry recorded morbidity, mortality, duration of operation, duration of ileus, length of hospital stay, and standard variables such as the patient's age, sex, diagnosis, indication for surgery and surgical procedure performed. Another goal at this institution was to reveal any differences in results between groups of patients who underwent total colectomy, segmental colectomy and diversion alone without resection.

Preoperative preparation was the same as for open procedures[9]. The techniques for laparoscopic colonic and rectal surgery have been described in detail elsewhere[10–12]. Briefly, all patients underwent standard mechanical cathartic bowel preparation in addition to receiving both oral and broad-spectrum parenteral antibiotics. The patient was placed in the supine modified lithotomy position in Allen

Table 1 *Procedures and indications for laparoscopic colorectal surgery*

Indication	No.	Procedure	No.
Mucosal ulcerative colitis	20	Total abdominal colectomy ($n = 32$)	
Cancer	12		
Familial adenomatous polyposis	6	Ileoanal anastomosis	23
		Ileorectal anastomosis	6
Crohn's disease	7	Ileostomy	3
Chronic diverticulitis	8	Segmental colectomy ($n = 32$)	
Polyp(s)	5	Right colectomy	10
Colonic inertia	4	Sigmoid colectomy	8
Radiation enteritis	2	Anterior resection	5
Faecal incontinence	5	Ileocolic resection	4
Prolapse	2	Hartmann's reversal	4
Ischaemic stricture	1	Abdominoperineal resection	1
Ileocaecal volvulus	1		
Lymphoma	1	Stoma creation	10
Total	74	Total	74

This paper is dedicated to the memory of Dr David G. Jagelman

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Table 2 *Results of laparoscopic colorectal surgery in 74 patients*

	Total colectomy (group 1; *n* = 32)	Segmental colectomy (group 2; *n* = 32)	No resection (group 3; *n* = 10)	Total (*n* = 74)
Duration of operation (h)	3·9 (2·5–6·5)	2·9 (1·5–5·5)	1·8 (1–2·5)	3·0 (1–6·5)
Duration of ileus (days)*	3·5 (2–7)	3·0 (2–7)	2·0 (1–4)	3·0 (2–7)
Duration of hospital stay (days)	8·1 (4–19)	7·0 (4–20)	6·0 (2–40)	7·0 (2–40)

Values are median (range). *Defined as the time until the patient passed flatus (or had a bowel movement) without nausea, vomiting or abdominal distension

Table 3 *Complications in 74 patients undergoing laparoscopic colorectal surgery*

Intraoperative	
Enterotomy or colotomy	4
Haemorrhage	
Trocar (epigastric)	2
Veress needle (aorta)	1
Dissection (iliac)	1
Heart block	1
Aspiration	1
Total	10 (14)
Postoperative	
Prolonged ileus	4
Intra-abdominal abscess	4
Wound infection	4
Urinary retention	1
Mallory–Weiss tear	1
Pleural effusion	1
Total	15 (20)
Reoperations	0

Values in parentheses are percentages

stirrups (Allen Medical, Bedford Heights, Ohio, USA) to allow transanal colonic access for colonoscopic identification of the site of the lesion, if needed.

The abdomen was prepared and draped in the standard fashion to provide wide exposure. The patient was then placed in a steep Trendelenburg position. After pneumoperitoneum had been established with carbon dioxide to a pressure of 15 mmHg, the Veress needle was removed and a 10/11-mm trocar placed through a 1-cm paraumbilical incision. A 0° laparoscope was then introduced through the port and all subsequent work performed under direct endoscopic visualization.

Colonic mobilization consisted of dividing the attachments and peritoneal reflections of the appropriate portion of the colon. The colonic mesentery was not routinely divided. However, for laparoscopic stoma creation the mesenteric vessels were divided with haemoclips or pretied Endoloops (Ethicon Endosurgery, Cincinnati, Ohio, USA). Intracorporeal bowel division was accomplished with a 60-mm linear cutting–stapling device (ELC-60; Ethicon). Introduction of the ELC-60 necessitated exchange of the 10/11-mm cannula for one of 18 mm at the preselected stoma site in the left iliac fossa. After bowel transection the proximal end was retrieved through the 18-mm cannula and the colostomy formed in the usual fashion[10].

During laparoscopically assisted procedures, after full mobilization of the appropriate portion of the bowel the remainder of the operation was performed through a small incision. After the bowel was delivered through this incision, division of the mesenteric vessels and bowel (and creation of anastomoses) were all performed in the standard fashion[11,12].

Results

Between August 1991 and June 1993, 74 patients underwent laparoscopic and laparoscopically assisted colorectal surgery. The 74 comprised 42 male and 32 female patients of mean age 45 (range 12–88) years. The procedures performed and indications for surgery are listed in *Table 1*. *Table 2* shows the results for the whole series, and the duration of surgery, ileus and hospital stay in group 1 (total abdominal colectomy), group 2 (segmental colectomy) and group 3 (diverting colostomy). There were no operative or postoperative deaths; however, 25 of the 74 patients (34 per cent) experienced at least one complication (*Table 3*). The most common postoperative complications were prolonged ileus, intra-abdominal abscess and wound infection. Anastomotic leakage was documented by radiographic studies in two of the four patients who developed an intra-abdominal abscess. The remaining two patients who developed an abscess suffered inadvertent enterotomies: one was recognized at the time of laparoscopy and the other discovered on day 4 after operation when a water-soluble enema revealed a full-thickness defect at the top of a defunctioned rectosigmoid pouch. This patient recovered slowly and required multiple antibiotics for persistent fever. She also required repeated percutaneous drainage of intra-abdominal abscesses and parenteral nutrition for prolonged ileus. She was eventually discharged home 40 days after operation in satisfactory condition.

Three procedures were abandoned and converted to open surgery before any dissection and/or mobilization of the colon. The reasons for termination of laparoscopy included an iliac arteriotomy, which was repaired, in one patient and epigastric vessel lacerations in two others; these required vessel ligation to control bleeding. All of these patients did well and were discharged home in satisfactory condition. No other patients required immediate conversion without some colonic mobilization or dissection.

Twelve patients were operated on for carcinoma. The mean number of lymph nodes dissected was 19 (range 3–84). There were three Dukes' A lesions, seven Dukes' B and two Dukes' C. All of these operations were performed with curative intent.

Discussion

Because of the pain, disability and cosmetic insult accompanying traditional open procedures, there has been a great impetus to develop less invasive methods. Laparoscopic surgery appears to be rapidly fulfilling this need. The question is thus no longer whether laparoscopic techniques have a place in general surgery, but rather what are the limits of their application.

The first laparoscopic general surgical procedure to be performed was appendicectomy. Initially these operations were carried out as incidental procedures during gynaecological surgery. However, in some centres laparoscopic appendicectomy has become the accepted treatment for acute appendicitis. In 1987, Mouret performed the first laparoscopic cholecystectomy[1]. This promising new technique rapidly spread after experience in America was reported by Spau and associates[2].

Critical appraisal confirmed the acceptable morbidity rate associated with the technique when performed by appropriately trained individuals. Other general surgical procedures followed and anecdotal reports demonstrated the technical feasibility of laparoscopic enteric and colorectal surgery[13–15]. However, several crucial differences between colorectal surgery and other laparoscopic general surgical procedures must be highlighted. First, all other procedures entail working in only one quadrant, thus limiting or eliminating the need to relocate instruments and personnel. Second, most operations are performed on small spaces or organs, enabling the use of smaller (5 mm) cannulas. All ports should be at least 10 mm for intestinal surgery as

Table 4 *Recent reports of laparoscopic colorectal surgery*

Reference	No. of patients	Type of colectomy	Mean (range) hospital stay (days)
Fleshman[7]	45	Laparoscopically assisted	5·8 (3–14)
Monson *et al.*[16]	33	Laparoscopically assisted	8·0 (5–14)
Larach *et al.*[17]	14	Laparoscopically assisted	7·2 (4–14)
Jacobs *et al.*[3]	19	Laparoscopic and laparoscopically assisted	4·6 (3–8)*
Phillips *et al.*[4]	51	Laparoscopic and laparoscopically assisted	4·6 (1–30)
Caushaj[6]	10	Laparoscopic	7·2 (5–14)
Present series	74	Laparoscopic and laparoscopically assisted	7·0 (2–40)†
Segmental resections	32	Laparoscopic and laparoscopically assisted	7·0 (4–20)†

*Data exclude two patients hospitalized for more than 1 week or who required reoperation. †Median (range)

frequent repositioning of both camera and instruments is necessary. Third, most of these procedures involve either no specimen extirpation or removal of a specimen so small that it is easily accomplished through a small cannula or small skin incision. Fourth, none of the other procedures requires anastomosis and thus none of the associated potentially adverse sequelae exists. Fifth, none of the other operations is undertaken for malignancy and so the question of recurrence after resection does not arise. All of these differences mandate that laparoscopic colorectal surgery always be meticulously performed. They also often demand that an incision of some size be made to allow for mesenteric division, bowel resection, anastomosis or specimen retrieval. Such factors may contribute to the lack of dramatic difference between the outcome and recovery period of open and laparoscopic colorectal surgery.

The present results are in many ways consistent with those of recently published reports (*Table 4*). In this study the overall median hospital stay was 7·0 days. However, unlike the series of Jacobs *et al.*[3], no exclusions were made in analysing the data. Again unlike all other published reports, the majority of operations were total rather than segmental colonic resections. When group 2 (segmental colectomy) is analysed independently, the duration of hospital stay is not significantly different from those cited by others. Similarly, when group 1 (total colectomy) is assessed, no differences are noted for length of ileus or duration of hospital stay compared with other patients undergoing laparoscopically assisted total colectomy[4,16]. Similar to the findings of Larach *et al.*[17], the present 34 per cent overall morbidity rate arose primarily in the early stages of development. It was also found that this advanced technology had a steep 'learning curve'.

Another problem with comparative results among different institutions is the definition of 'resolved ileus' and the treatment of these patients before complete resolution. Some confusion may result from the fact that advocates of laparoscopic surgery may treat patients differently after laparoscopy than after standard laparotomy. Specifically, some send patients home on a clear fluid diet with instructions to advance their own diet as tolerated[18]. Binderow *et al.*[19] in a prospective randomized trial demonstrated a trend towards earlier discharge when patients receiving standard laparotomy were allowed to eat a regular diet on the first day after operation. The advent of laparoscopic surgery may alter management of 'standard' patients in the future.

A question of paramount importance is lymph node status and the appropriateness of minimally invasive technology for the treatment of colorectal carcinoma. The current standard of care for the treatment of large bowel cancer is abundant excision of lymph node-bearing tissue. No study has demonstrated that patients have a longer survival when an increased number of positive lymph nodes is removed. Therefore, it is not imperative that studies are compared with respect to the number of nodes harvested. Of significant importance, however, is the fact that there have already been numerous reports of recurrence at the site of cannula insertion after laparoscopic resection of colonic tumours[20–25]. These early reports emphasize the need for established registries to evaluate prospectively variables related to laparoscopic colorectal surgery.

Compromise of established surgical principles cannot be accepted to facilitate technique; technical advances must be made within the constraints such principles impose. These preliminary results are certainly not encouraging; however, it is hoped that continued development of both laparoscopic technology and technique will be associated with improved benefits for patients. Randomized trials will be necessary to demonstrate advantages over open surgery of laparoscopic colonic and rectal procedures. To date no such advantage can be substantiated.

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Announcement

The British Journal of Surgery Society SRS Prize

The British Journal of Surgery Society is to make a generous annual donation of £500 to the Surgical Research Society to be used as a prize. The Committee of the SRS, on behalf of its membership, is pleased to acknowledge the gift with gratitude.

The SRS Committee has decided that the prize will be awarded for the best paper published in the *BJS* that originates from an SRS presentation in the preceding year. The Committee of the SRS will judge these papers at its January meeting and the prize will be announced and presented at the dinner of the SRS.

The SRS is pleased to maintain close ties with the Journal. Two months each year are special SRS issues and contain most of the papers from presentations made to the SRS. It is hoped that this prize will encourage more presenters of SRS papers to prepare manuscripts without detracting from the principle of the SRS to enjoy receiving reports of work in progress. Papers not making publication in the SRS issues *will not be ineligible* and the winner of the Patey Prize *may* submit a paper and be equally eligible. It should be noted that any paper submitted as a result of presentation to the SRS passes through the same rigorous process of referee analysis and editorial criticism by the Journal; publication is not guaranteed.

SRS authors should identify the January or July meeting of the presentation on the submitted manuscript. Papers will automatically be collected and reviewed for the prize. Those already published in 1993 issues will automatically be included for consideration of the prize to be awarded for the first time in January 1994.

'Thank you' to The British Journal of Surgery Society for fostering and encouraging surgical research.

J. R. Farndon

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New technique for sigmoid colectomy

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A combination of laparoscopic and rectoscopic procedures has enabled complete resection of the sigmoid colon and eliminated the need for minilaparotomy when constructing the anastomosis or withdrawing the specimen. This combined procedure was performed in different ways in a series of animal models until the definitive technique had been standardized. These techniques were then successfully used in 15 consecutive medium-sized pigs. Histological evaluation of the specimens, including the anastomosis (examined 2–3 weeks after operation) confirmed the efficacy and safety of the method.

Laparoscopic techniques have been used to carry out highly selective vagotomy, nephrectomy and colonic resection. Currently, endoscopic colonic resections are laparoscopically assisted: endoscopic preparation of the bowel is combined with anastomosis or withdrawal of the specimen carried out through a minilaparotomy[1–5]. Laparoscopy and rectoscopy allow completion of the endoscopic resection of the left or sigmoid colon, eliminating the need for minilaparotomy.

A combined laparoscopic–rectoscopic approach to sigmoid colectomy was developed and performed in different animal models during a 1-year *in vivo* study approved by the local committee for animal experiments. The procedure is illustrated and discussed.

Materials and methods

Operations were performed in three species: seven minipigs, nine sheep and 16 medium-sized pigs. Seventeen animals were used to determine the optimal animal model, appropriate apparatus and definitive operative technique. The procedure (as an endoluminal or extraluminal variant) was then performed in 15 medium-sized pigs in a standardized animal trial.

Animals were fasted for 3 days and given a preoperative enema. Antibiotic prophylaxis was not used. All animals were operated on under general anaesthesia with central venous catheterization and cardiac monitoring. After operation, fasting continued for 1–2 days. The animals were killed 2–3 weeks after operation and the specimen, including the anastomosis, was sent for histological study.

Operative procedure

The surgeon and camera operator stood to the right and the assistant to the left of the animal. The video equipment was positioned on the assistant's left. After establishing pneumoperitoneum, four ports were placed in the lower abdomen (*Figure 1*). A 10-mm cannula, inserted to the right of the umbilicus, was used to introduce a 50° telescope (Richard Wolf, Knittlingen, Germany). An 11-mm trocar and a 5-mm silicon cannula were introduced into the lower right quadrant: the first was an operative port placed about 7 cm below and laterally to the umbilicus; the second, close by the anterior iliac spine, allowed insertion of a curved grasper. A 5-mm cannula for graspers was placed in the left lower abdomen, opposite the 11-mm port. Suprapubic catheterization of the bladder was performed and a catheter left *in situ*. The operating table was placed in a mild Trendelenburg position and tilted to the right.

The sigmoid colon was grasped and fixed to the abdominal wall by means of two slings passed through the mesocolon with forceps. Each end of the sling was held by a 3-mm needle-holder introduced into the peritoneal cavity through two small incisions in the left lower quadrant. The vessels were ligated and divided. A polydioxanone extracorporeal slipknot developed for monofilament material (*Figure 2*) was used for vessel ligature. The slings were removed and a modified transanal endoscopic microsurgery rectoscope (Richard Wolf)[6,7] (*Figure 3*) introduced up to the rectosigmoid junction.

Endoluminal procedure. The anvil of a Proximate ILS 29-mm stapler (Ethicon, Norderstedt, Germany) was inserted into the left colon via a custom-made introducer (*Figure 4*). Two polydioxanone 0 slipknots were tightened around the sigmoid colon at its proximal and distal levels, keeping the introducer inside. The anvil was fixed to the descending colon by a polydioxanone 2/0 slipknot and the sigmoid colon divided between ligatures. A cable-binding technique was specially developed to fix the anvil safely. This was prelocked extracorporeally (*Figure 5*) and tightened around the colon by means of a special pusher, reinforcing the polydioxanone ligature. After division of the proximal rectum the specimen, fixed around the introducer, was withdrawn through the rectoscope (*Figure 6*). The loop of another prelocked cable-binder was kept around the rectum, held with graspers, and the rectoscope withdrawn and exchanged for the stapler shaft under laparoscopic control. The spike of the stapler was advanced through the open stump and the cable-binder tightened around it. Any excess tissue was carefully resected. Using a new anvil-holder, the anvil was inserted into the shaft and the stapler closed and fired.

Extraluminal procedure. Two polydioxanone 0 slipknots were tightened around the sigmoid colon at its proximal and distal levels. A small cut was made on the upper rectum, just below the distal ligature, and on the left colon, just over the proximal ligature. The anvil of a Proximate ILS 29-mm stapler was introduced up to the left colon, letting the introducer pass through the two cuts (*Figure 7a*) by gently pushing and twisting it through the operative rectoscope. A polydioxanone slipknot was tightened around the left colon to fix the anvil and the introducer withdrawn. The sigmoid colon was divided,

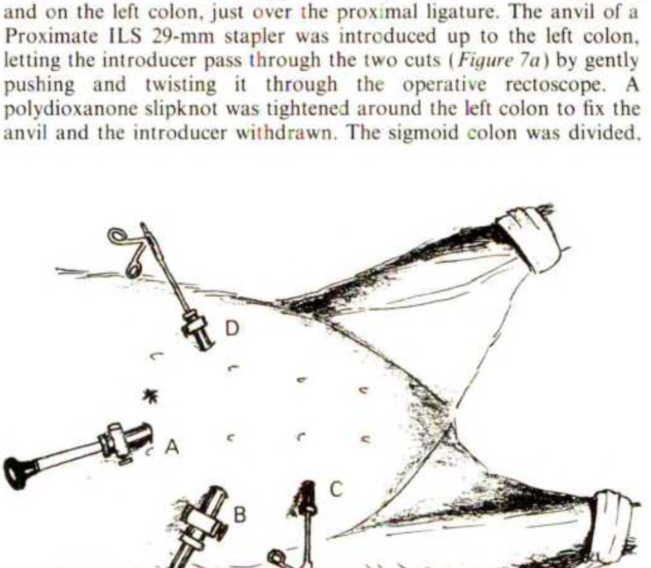

Figure 1 *Positions of the introduction sites. A, 10-mm port for the telescope; B, 11-mm port for operative instruments; C, 5-mm silicon cannula for the curved graspers; D, 5-mm port for grasping forceps*

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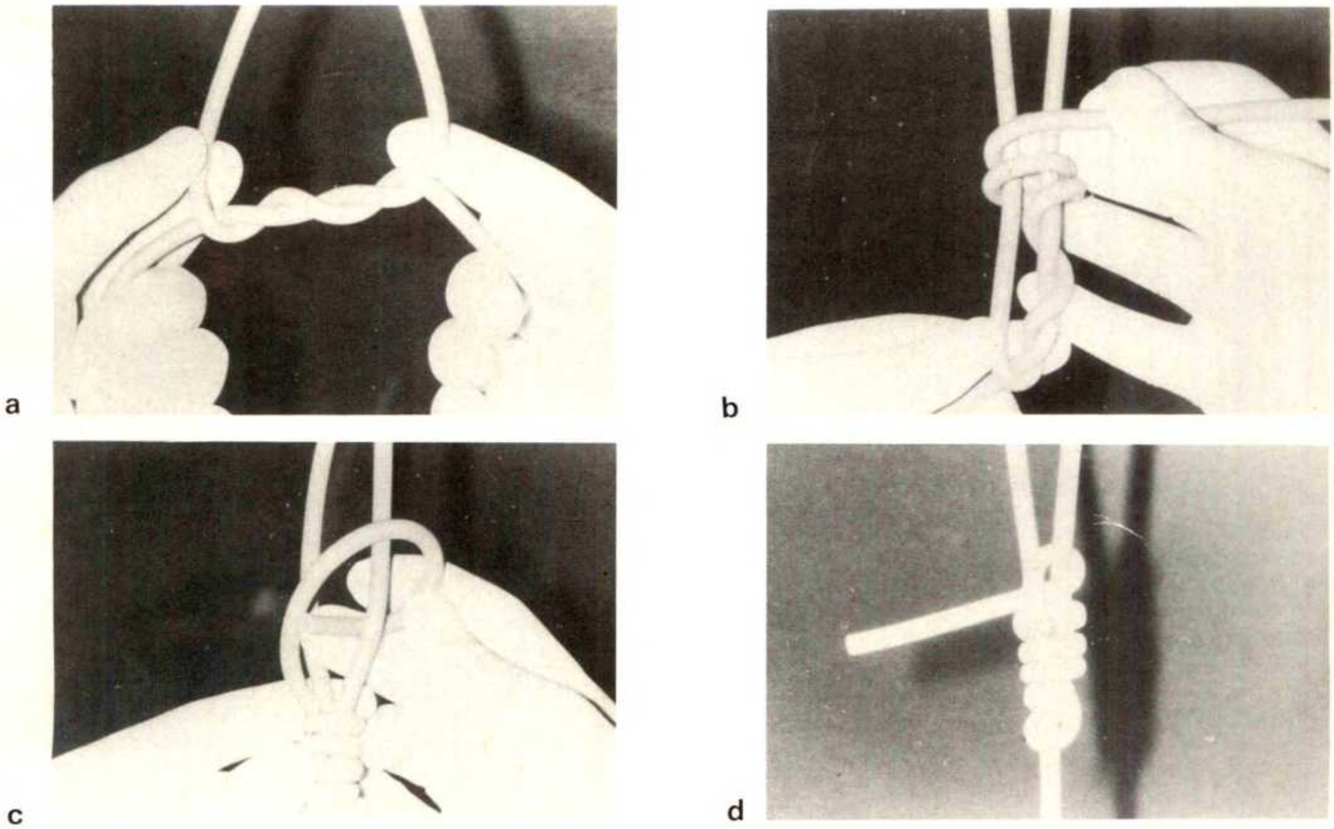

Figure 2 *Technique for the Melzer–Bueß knot.* **a** *First, a surgical knot was made;* **b** *one head of the thread was then twisted twice around the other head, according to the Roeder technique;* **c, d** *the knot was completed by a double-blocking passage*

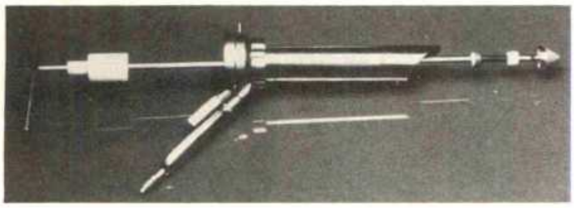

Figure 3 *The Bueß operative rectoscope with the loaded anvil-introducer*

completing the cut between the ligatures. With two graspers holding the upper rectum, the distal cut was completed and the specimen grasped by a forceps inserted through the rectoscope and withdrawn (*Figure 7b*). The spike of the stapler was advanced *per rectum* under laparoscopic control and the cable-binder tightened. A second prelocked cable-binder was tightened around the proximal stump to ensure fixing of the anvil. The anvil was inserted into the shaft, and the stapler closed and fired.

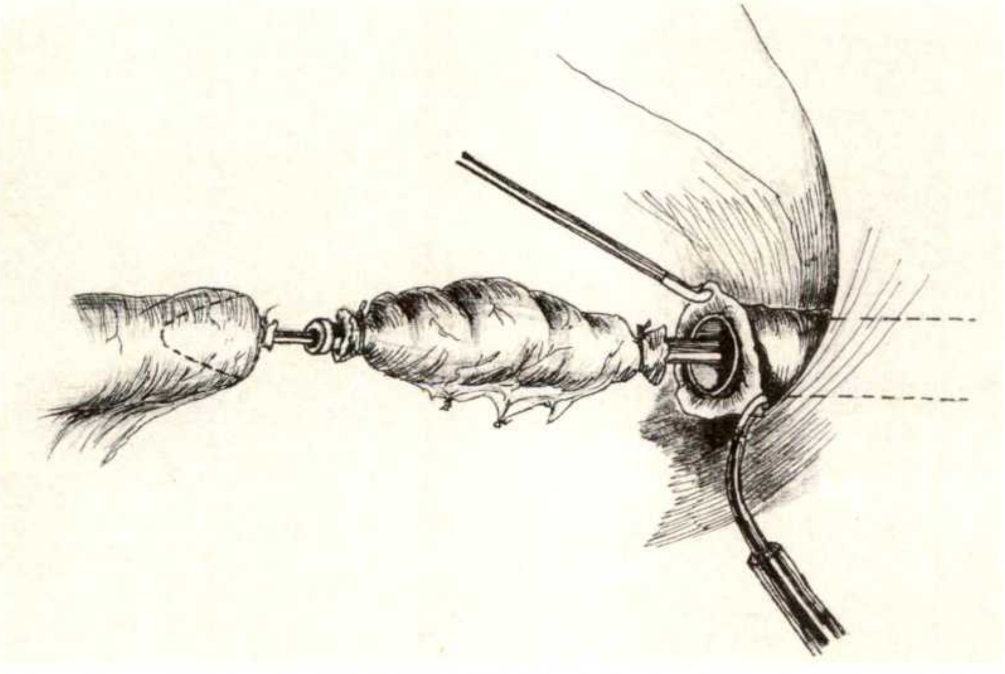

Figure 4 *The anvil was introduced up to the proximal sigmoid colon (endoluminal procedure); the proximal sigmoid was divided between ligatures. A ligature on the proximal stump fixed the anvil temporarily*

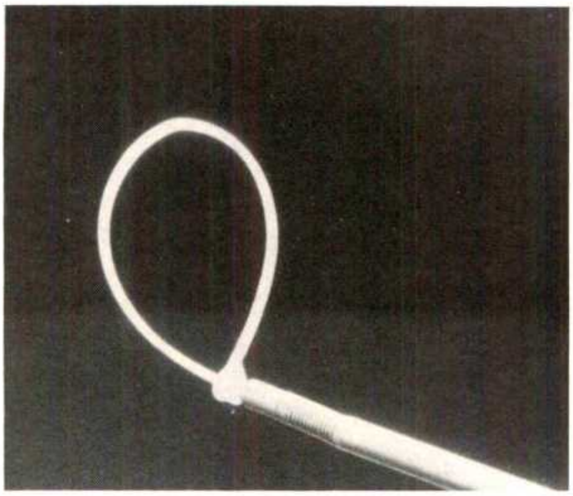

Figure 5 *A prelocked cable-binder inserted into the special pusher. This is a manufactured plastic device with ratchets that do not slip back when tightened*

Results

The mean duration of surgery was 135 (range 100–180) min.

All animals had an uneventful postoperative course with no clinical signs of sepsis. Autopsy in one animal showed a localized encapsulated fluid collection with a few adhesions. In three animals there was a small area of dehiscence with histological signs of abscess formation. These abnormalities were found in the first five animals to be operated on.

Discussion

The main technical difficulties of the laparoscopic approach to left colectomy and sigmoidectomy are formation of the anastomosis and removal of the specimen. Development of the anvil-introducer and the cable-binding technique overcame such problems.

The anvil-introducer is a device with an air-proof system that is fixed to the rectoscope; it avoids any air leakage once the bowel has been opened.

The cable-binding technique has been developed to avoid the intracorporeal purse-string ligature of the two stumps. This

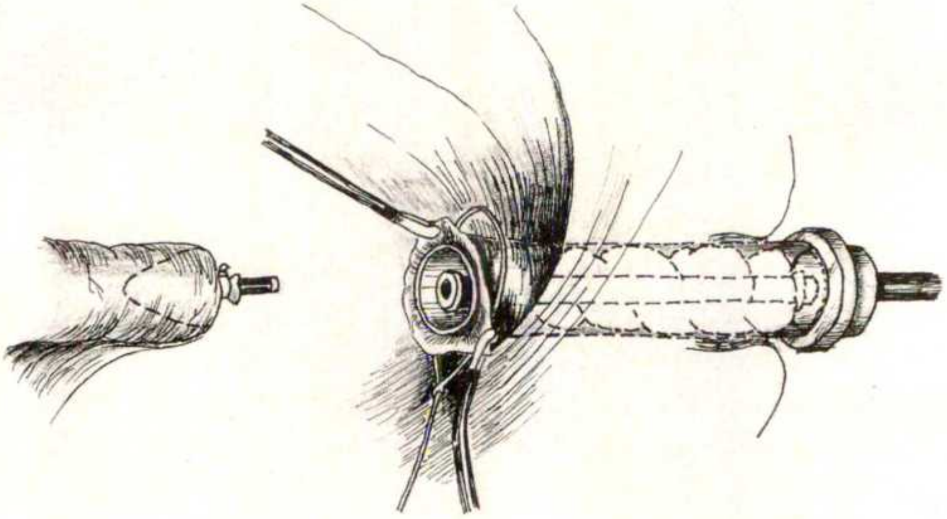

Figure 6 *Specimen retrieval during the endoluminal procedure. A prelocked cable-binder was kept around the distal stump while the resected bowel was withdrawn through the rectoscope via the anvil-introducer*

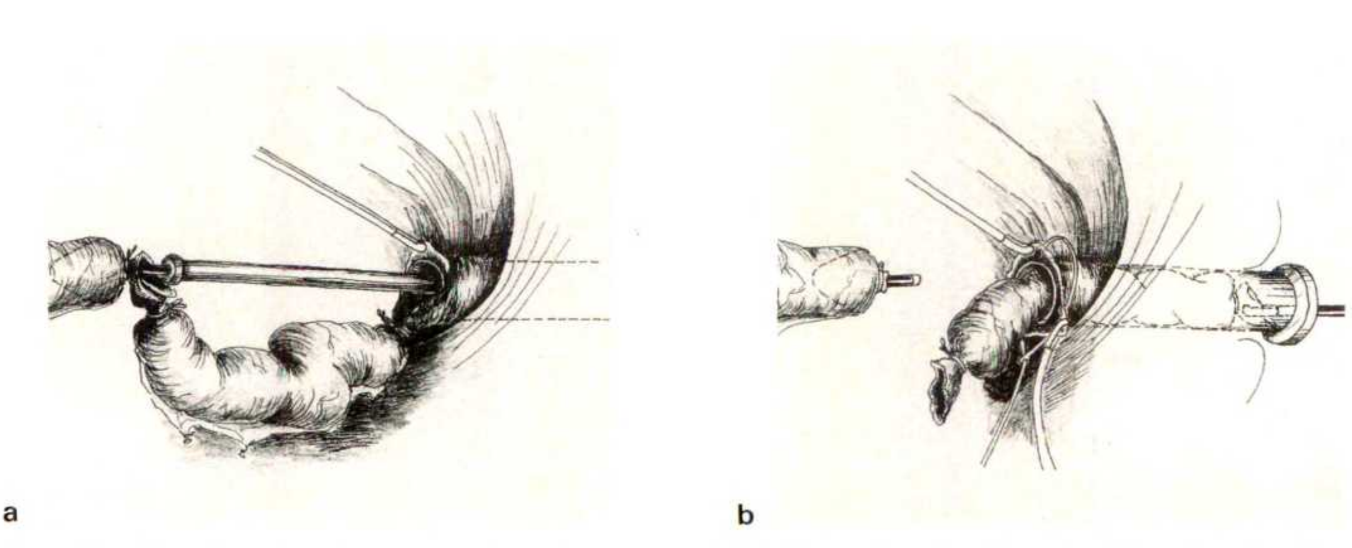

Figure 7 **a** *Introduction of the anvil during the extraluminal procedure: the introducer was gently pushed through two small cuts at the level of the proximal rectum and sigmoid colon.* **b** *Removal of the specimen by means of a grasping forceps inserted through the rectoscope (extraluminal procedure)*

technique is difficult and time consuming when performed laparoscopically. The use of a prelocked cable-binder allows fast and tight closure of the stumps. The use of endoloops or slipknot ligatures is not as safe as that of cable-binders, particularly in the closure of a short rectal stump.

Careful freeing of colonic and rectal stumps from the mesocolon is mandatory: the use of a 50° angled telescope is helpful for a complete check of both sides of the intestinal wall before and after closure of the stapling device.

The extraluminal variant of the combined sigmoidectomy avoids contact between the anvil-introducer and the tumour in case of suspected or proven neoplasm, and such a technique brings the anvil up to the proximal stump in the case of stenosing diverticulitis.

Because of the diameter of the rectoscope, removal of tumours up to 4 cm in size can be performed. Benign and soft neoplasms larger than 4 cm that can be compressed can also be removed.

Laparoscopic lymphadenectomy is possible and safe[8–10] as ligature of the inferior mesenteric vessels is feasible, but extensive and radical lymph node dissection may not be curative.

Clinical application of this method is under way in patients with benign and malignant tumours and complications of diverticular disease.

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Change towards earlier stage at presentation of colorectal cancer

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A study was carried out to investigate the change in stage at presentation of patients with colorectal cancer over 10 years. Cases were identified from the control group of subjects enrolled into a randomized controlled study based on Haemoccult screening for colorectal neoplasia. Of 405 subjects in the control group (presenting with symptomatic colorectal cancer, 206 presented before 1989 and 199 since then. The number of patients with Dukes' stage A carcinoma diagnosed since 1989 rose from 21 (10·4 per cent) to 35 (18·1 per cent); this change occurred for rectosigmoid tumours (9·9 per cent before 1989, 28 per cent after 1989) but not for colonic cancer (10·9 per cent before 1989, 11·5 per cent thereafter). An increase in the proportion of patients with symptomatic early-stage rectosigmoid cancer has been observed in the past 10 years. No such change occurred in those with colonic cancer. This may reflect a change in awareness of the disease and its symptoms by patients and general practitioners.

More than 17 300 people died from colorectal cancer in the UK in 1988, the disease accounting for 12 per cent of all cancer-related deaths[1].

Prognosis is determined largely by the extent of spread of the tumour at diagnosis. Three large studies of consecutive unselected patients with colorectal cancer presenting to non-specialist hospitals have shown crude 5-year survival rates of 25·8–27 per cent. This reflects the substantial proportion of patients presenting with advanced disease, only 5·7–6·3 per cent having Dukes' stage A cancers[2–4].

Cuthbert Dukes observed that:

> 'there is no doubt that the proportion of A and B cases could be increased by earlier diagnosis. The relative proportion of A, B and C cases in the future will provide a delicate indication as to whether or not propaganda for the earlier recognition of malignant disease has been successful in respect of the lower end of the alimentary tract'[5].

Vellacott *et al.*[6] reported, for a 16-year period to 1986, a rising detection rate of symptomatic Dukes' A tumours, and concluded that this was attributable largely to improved provision and quality of diagnostic facilities, increasing use of double-contrast barium enema and availability of a local open-access flexible sigmoidoscopy service.

A large randomized controlled trial[7] of faecal occult blood (FOB) testing in the early detection of colorectal cancer has been taking place in Nottingham since 1981. The population is randomized to test and control groups. The test group is educated as to the importance of rectal bleeding and offered FOB testing, whereas those in the control group are identified but not contacted. The stage at presentation of colorectal cancer in the control group should mirror that of the whole population and the aim of this study has been to describe the change in stage at presentation of these subjects in Nottingham over the past decade.

Patients and methods

Subjects aged 50–75 years were identified from general practitioner (GP) registers. After stratification by age and sex, they were randomized by household into a test group (sent FOB tests) and a control group (no tests). The development of colorectal neoplasia (not just that presenting for surgery) in both groups was monitored by regular scrutiny of the pathology records of the Nottingham hospitals, by the Trent Region Cancer Registry and through information supplied by GPs. The Family Health Services Authority notified the study of those leaving the area and these patients were 'flagged' at the National Health Service Central Registry.

The test group received an explanatory letter from their GP stressing the importance of early detection and stating that 'rectal bleeding is an important symptom of large bowel disease ... including cancer'. A Haemoccult (Rohm, Wietarstadt, Germany) test pack was enclosed, which they were invited to complete and return. Those doing so were termed 'acceptors' and those not responding or returning the tests uncompleted were 'refusers'. The refusers present with symptomatic disease in the same way as the control subjects. Control subjects were not contacted but were identified and followed for the development of colorectal cancer as described above. To minimize 'contamination' of the control group, publicity about the study was kept to a minimum.

Cancers were staged according to Dukes' classification[8], to which was added stage 'D' for patients presenting with distant metastases or locally irresectable disease[9]. When calculating the proportion of cancers at any pathological stage, unstaged tumours were excluded from the denominator.

Rectosigmoid tumours are defined as those within 20 cm of the anal verge, the remainder being colonic.

The study started in 1981 and data were analysed for cancers presenting to 1 September 1991. An arbitrary date of 31 December 1988 was used to divide the study period into two approximately equal halves with respect to person-years of observation and cancers diagnosed. The section before 1989 covered a much longer time period because of slow recruitment and a gap between the pilot study and the start of the main trial.

Statistical comparisons were made using the χ^2 test.

Results

Since 1981, 155 101 subjects from 92 general practices were recruited into the study, 77 670 in the control group. From the test group, 34 448 patients (44·5 per cent) refused the offer of screening.

Of the control group subjects, 405 (5·2 per 1000) presented with symptomatic colorectal cancer: 206 were diagnosed before 1 January 1989 and 199 since then. The earlier period represented 178 476 (49·4 per cent) of the total 361 136 control patient study-years. The two groups were well matched for age and sex (*Table 1*).

There was a significant increase in the proportion of Dukes' stage A cancers diagnosed since 1989 from 10·4 to 18·1 per cent ($\chi^2 = 4{\cdot}77$, 1 d.f., $P < 0{\cdot}05$), and a fall in those presenting with distant metastases from 27·7 to 17·6 per cent ($\chi^2 = 5{\cdot}73$, 1 d.f., $P < 0{\cdot}02$). The proportion of patients presenting with localized

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Table 1 *Demographic data*

	Controls				Refusers			
	Colon		Rectosigmoid		Colon		Rectosigmoid	
	Before 1989	After 1989	Before 1989	After 1989	Before 1989	After 1989	Before 1989	After 1989
Total	102	116	104	83	66	49	51	41
No. male*	49 (48·0)	53 (45·7)	67 (64·4)	51 (61)	33 (50)	22 (45)	36 (71)	27 (66)
Mean (range) age (years)	67 (44–82)	68 (52–83)	67 (51–82)	66 (51–81)	69 (52–80)	70 (52–83)	68 (52–80)	69 (55–82)

*Values in parentheses are percentages

Table 2 *Cancer stage distribution among control group subjects*

	Colon		Rectosigmoid		Total	
Dukes' stage	Before 1989	After 1989	Before 1989	After 1989	Before 1989	After 1989
A	11 (10·9)	13 (11·5)	10 (9·9)	22 (28)	21 (10·4)	35 (18·1)
B	33	47	25	28	58	75
C	28	30	39	19	67	49
'D'	29 (28·7)	23 (20·4)	27 (26·7)	11 (14)	56 (27·7)	34 (17·6)
Unstaged	1	3	3	3	4	6
Total	102	116	104	83	206	199

The proportion at each stage was calculated as a percentage of the total number of staged cancers. Values in parentheses are percentages

Table 3 *Cancer stage distribution among refuser group subjects*

	Colon		Rectosigmoid		Total	
Dukes' stage	Before 1989	After 1989	Before 1989	After 1989	Before 1989	After 1989
A	4 (6)	2 (4)	13 (25)	9 (25)	17 (14·5)	11 (13)
B	24	13	16	10	40	23
C	15	10	9	8	24	18
'D'	23 (35)	23 (48)	13 (25)	9 (25)	36 (30·8)	32 (38)
Unstaged	0	1	0	5	0	6
Total	66	49	51	41	117	90

The proportion at each stage was calculated as a percentage of the total number of staged cancers. Values in parentheses are percentages

disease (stage A or B) rose from 39·1 to 57·0 per cent (χ^2 = 12·65, 1 d.f., P < 0·001) (*Table 2*).

After 1989, 41·7 per cent of tumours (83 of 199) were in the rectosigmoid – a non-significant decline from 50·5 per cent (104 of 206). These subgroups of patients with colonic and rectosigmoid carcinoma were similarly well matched for age and sex for the two time periods (*Table 1*). There was a significant increase in the proportion of Dukes' A rectosigmoid cancer from 9·9 to 28 per cent (χ^2 = 7·20, 1 d.f., P < 0·01), whereas the proportion of Dukes' A colonic cancers remained static with time (10·9 per cent before 1989, 11·5 per cent thereafter). The proportion of rectosigmoid cancers presenting at stage 'D' decreased from 26·7 to 14 per cent (χ^2 = 4·54, 1 d.f., P < 0·05) (*Table 2*).

The effect of patient and GP awareness was assessed in the test group subjects. Refuser subjects in all screening studies have low levels of health awareness[10]. It is to be expected that this will be reflected in a high proportion of advanced cancers and relatively few stage A tumours. Of 114 staged colonic cancers diagnosed in subjects who did not accept the Haemoccult test, six (5·3 per cent) were Dukes' stage A and 46 (40·4 per cent) had distant metastases or an irresectable primary. Twenty-two (25 per cent) of the 87 staged rectosigmoid cancers in refusers were at stage A while only 22 had stage 'D' disease. At neither site was there a significant difference between the proportions in the two time periods, but patients with rectosigmoid cancer presented significantly more often at stage A (χ^2 = 9·61, 1 d.f., P < 0·01) and less often at stage 'D' (χ^2 = 5·00, 1 d.f., P < 0·05) than their counterparts with colonic cancer (*Table 3*).

Discussion

These results could be explained by: (1) a trend towards less virulent disease; (2) improved radiology and/or endoscopy facilities; or (3) increased awareness of the disease and its symptoms by patients and GPs. If the first were true then the change should occur equally for rectosigmoid and colonic carcinoma. If the second were important, given that most rectosigmoid cancers are first diagnosed by digital examination and/or rigid sigmoidoscopy[6], the change would be more likely in those with colonic tumours. The polypectomy rates in the two time periods may be taken as an indicator of the number and quality of diagnostic examinations performed. Between 1981 and 1989, seven carcinomas were treated by polypectomy in the control group subjects compared with four after 1989 (χ^2 = 0·41, 1 d.f., P = 0·52). The numbers of adenomas treated by polypectomy were 73 and 78 respectively for the two periods (χ^2 = 0·03, 1 d.f., P = 0·85). These data are consistent with no change in the quality of diagnostic investigation with time.

Finally, an important symptom of rectal cancer is bleeding, occurring in 70 per cent of rectal but in only 35 per cent of colonic cancers[2]. Refusers differ from controls in having received the letter of invitation and, in spite of failure to complete and return the tests, the message from the letter may have been absorbed. A further potentially important factor is the impact of the study on educating local GPs. In 1979, doctor-related delay to diagnosis occurred in up to one-third of colorectal cancers and was longer for rectosigmoid lesions (15·3 weeks) than for colonic tumours (11·2 weeks)[11]. Rectal examination is carried out in general practice to a varying extent[12]. A 10-year review of GP awareness of colorectal cancer from 1978 to 1988 found that fewer than half of all digitally palpable rectal cancers had been noted by the GP (8 per cent of patients being referred without having had a rectal examination)[13]. A questionnaire survey of Nottinghamshire and Leicestershire GPs is currently addressing questions of knowledge and awareness of the disease in the study area and a neighbouring control area.

It is likely that the changes observed result from increasing awareness of the disease and its symptoms. A similar trend towards earlier diagnosis has recently been reported for gastric cancer[14]. These encouraging trends may reflect nationwide change and probably relate to local special interest in the diseases in question.

Acknowledgements

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Follow-up after inguinal herniotomy or surgery for hydrocele in boys

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A retrospective review of 556 boys who had undergone inguinal herniotomy or surgery for hydrocele was carried out to assess the value of early routine postoperative follow-up. Of 386 children given an appointment, 319 (82·6 per cent) attended. The testis was no longer palpable in the normal scrotal position in 12 boys; eight were normal on further review and four required orchidopexy. Six hydroceles, all of which resolved, and four contralateral hernias were detected. Nineteen boys (4·9 per cent) were referred later with recurrent hernia (two patients), ipsilateral high testis (two), or contralateral hernia or hydrocele (15). Of 170 children not given a routine appointment, ten (5·9 per cent) were subsequently referred back with a transient hydrocele (two) or a contralateral hernia (eight). After a total of 440 appointments, eight boys (1·8 per cent) were found to have a significant abnormality. The rate of referral back to hospital was similar in both groups. Early discharge would make more efficient use of outpatient resources without significantly affecting overall outcome.

The policy of routine follow-up after all surgical operations has been superseded by a more selective approach. Many surgeons continue to follow boys who have undergone inguinal herniotomy or ligation of a patent processus vaginalis because of possible damage to the vas deferens and vessels, either by hernia incarceration or during dissection, and the consequent risk of testicular atrophy or malposition[1]. A difference in attitudes to routine follow-up after such operations during the past 5 years has allowed a retrospective examination of its value.

Patients and methods

Boys who underwent inguinal herniotomy or ligation of a patent processus vaginalis between August 1986 and December 1990 were identified from the hospital operation register. One surgeon did not arrange routine outpatient follow-up appointments. Clinical characteristics in the case notes were reviewed: age at operation, incarceration of hernia requiring reduction by taxis, side of hernia or hydrocele, grade of surgeon, whether a follow-up appointment was made, attendance for review, findings at the outpatient clinic and any subsequent related problem for which the patient attended. Boys who had undergone orchidopexy for a simultaneous ipsilateral undescended testis were excluded. The two groups were compared by the χ^2 test using Statistics (Blackwell Scientific Software, Oxford, UK).

Results

A total of 559 boys were identified as having undergone inguinal herniotomy or processus vaginalis ligation. The case notes of one child could not be located and orchidopexy had been performed on two, leaving 556 patients for analysis. Outpatient follow-up appointments were given to 386 boys and 170 were discharged to general practitioners. There was no difference between the two groups with regard to age at operation, incarceration at the time of presentation, side of operation or grade of operating surgeon (*Table 1*).

Some 319 boys (82·6 per cent) attended for review after a median interval of 6 (range 3–15) weeks and after a mean of 1·1 (range 1–5) appointments. Of those who attended, 158 (49·5 per cent) were seen by the surgeon who performed the operation. In 12 boys the testis was no longer palpable in the normal scrotal position; on further review, between 3 and 6 months later, eight were normally positioned and four required orchidopexy. Six testes were surrounded by a hydrocele but these resolved after 3 months. Four contralateral hernias were detected. Nineteen boys (4·9 per cent) were later referred back: two with recurrent hernia, two with a high testis and 15 with a contralateral hernia or hydrocele (*Table 2*).

Of the 170 boys not given a routine follow-up appointment, ten (5·9 per cent) were subsequently referred back: two with an

Table 1 *Details of 556 boys who underwent inguinal surgery*

	Follow-up ($n = 386$)	No follow-up ($n = 170$)	χ^2	d.f.	P
Age at operation (months)					
< 1	14	5	0·174	2	0·92
1–18	161	72			
> 18	211	93			
Incarceration at presentation	43	19	0·018	1	0·89
Side of operation					
Right	303	118	1·36	1	0·24
Left	143	70			
Operating surgeon					
Consultant	98	46	0·096	1	0·75
Senior registrar or registrar	288	124			

Table 2 *Abnormalities after inguinal surgery related to follow-up*

	Follow-up ($n = 386$)	No follow-up ($n = 170$)
Malposition requiring orchidopexy	6* (1·6)	0 (0)
Transient hydrocele	6 (1·6)	2 (1·2)
Contralateral hernia or hydrocele	19 (4·9)	8 (4·7)
Recurrent hernia	2* (0·5)	0 (0)
Testicular atrophy	1 (0·3)	0 (0)

Values in parentheses are percentages. *Junior surgeons did not predominate in these groups

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ipsilateral hydrocele, one of which resolved spontaneously, and eight with a contralateral hernia.

Discussion

From 440 appointments only eight patients with significant abnormalities requiring further intervention were identified, a yield of one abnormality for every 55 appointments offered. This does not represent efficient use of outpatient resources.

The potential benefit of routine follow-up after inguinal surgery in boys is the detection of iatrogenic testicular malposition or atrophy, contralateral hernia or hydrocele, and wound complications. This must be balanced against the use of finite outpatient resources, the inconvenience to patients and parents, the child's anxiety of returning to hospital and the false reassurance that is felt if a related problem subsequently develops.

Follow-up at 6–12 months might reduce the number of self-limiting problems that are seen, such as transient hydrocele, and allow better assessment of testicular atrophy and malposition, but would probably lead to a higher non-attendance rate.

Five of the six boys who subsequently required orchidopexy were under 18 months of age at the time of surgery. Increased awareness about testicular position and early orchidopexy[2], by parents and primary healthcare teams, might allow these children to be referred back if discharged without early postoperative follow-up.

Routine follow-up allows audit of results[3], but only 50 per cent of the present patients who attended were reviewed by the operating surgeon. Only 25 per cent of wound complications following adult elective hernia repair are detected at outpatient follow-up and a rigorous community-based postoperative surveillance programme is needed to collect accurate and comparable information for audit[4].

The possible complications of inguinal surgery should be outlined in an information sheet given to parents and in a discharge summary sent to the general practitioner. An invitation to discuss or review any specific problem would reduce unproductive outpatient visits for most patients and improve the service to others by making available additional outpatient time.

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Total pelvic exenteration: a justified procedure

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Twenty patients with advanced primary or locally recurrent pelvic tumours treated by total pelvic exenteration are described. There were no operative or postoperative deaths. The most frequent postoperative complications appeared to be related to previous irradiation. Four patients developed non-fatal intestinal complications within 30 days of operation that required further surgery. After a mean follow-up of 19 months the crude 2-year survival rate was 40 per cent. This procedure is judged to be useful in a selected group of patients.

Mutilating radical resections such as total pelvic exenteration are occasionally justified. This procedure can be used to remove locally advanced pelvic tumours *en bloc* with the rectum and sigmoid colon, bladder, distal ureters and internal reproductive organs. It is sometimes possible to perform a modified procedure by saving the anal sphincters or partially preserving the bladder without compromising radicality[1-6].

The best candidates for total pelvic exenteration are patients with a locally invading central pelvic tumour without evidence of distant metastases. Without this procedure these patients will have a miserable death as a result of internal fistula, bleeding, pain caused by tumour invasion into the lumbosacral plexus, and a rectal syndrome. Total pelvic exenteration may offer them a chance of local tumour control with improved quality of life and, possibly, cure[4-7]. However, this procedure may result in serious morbidity and even death, and the question of whether it is worth while has to be asked. This study reports experience with 20 patients.

Patients and methods

Between August 1981 and September 1990, 20 patients underwent total pelvic exenteration in the Department of Surgical Oncology. They comprised 15 women and five men of median age 58 (range 38-70) years. Disease in each patient was staged by physical examination, chest radiography, thoracic and abdominal computed tomography, urography and cystoscopy.

The indications for total pelvic exenteration are summarized in *Table 1*. In nine patients the procedure was carried out for primary pelvic malignancy and in 11 for recurrent disease. The mean interval between the first treatment for cancer and total pelvic exenteration in patients with recurrence was 24 months. Previous surgery included anterior resection in three patients, abdominoperineal resection in one and hysterectomy in three.

Thirteen of the 20 patients had been treated previously with radiotherapy of the pelvic organs in doses ranging from 40 to 65 Gy with conventional fractionation.

The original technique of total pelvic exenteration as described by Brunschwig[8] was performed in nine patients. In the other 11 a modified procedure was carried out. In seven patients a very small rectal stump beneath the levator muscle was left *in situ* (Hartmann's procedure) and in four other patients colorectal anastomosis was performed. In 17 patients total cystectomy was needed. Urinary diversion was achieved by means of an ileal conduit as described by Bricker[9] in 11 patients and by means of a sigmoid conduit in six. In three patients partial cystectomy with a U shaped ileocystoplasty and ureteric reimplantation was performed, with ureterointestinal anastomosis using the Leadbetter technique.

Subsequently, four patients also underwent inguinal lymph node dissection. In two patients the groin dissection was part of the primary strategy in the treatment of recurrent vaginal and rectal cancer. In the other two this dissection was carried out for inguinal node metastases that developed during follow-up at 5 and 6 months after pelvic exenteration for vaginal melanoma.

Disease in patients with colorectal carcinoma was staged by the Dukes-Astler-Coller classification[10]. Survival was expressed by a Kaplan-Meier life-table.

Table 1 *Summary of indications for total pelvic exenteration*

Indication	No. of patients
Rectal carcinoma	
Primary	5
Recurrent	4
Cervical carcinoma	
Primary	1
Recurrent	5
Vaginal carcinoma	
Primary (melanoma)	2
Recurrent	1
Recurrent endometrial carcinoma	1
Bladder carcinoma	1
Total	20

Results

The mean operating time was 5·5 (range 5-7) h and the mean blood loss 2900 (range 1500-6500) ml. The mean postoperative hospital stay was 27 (range 13-90) days.

Although some patients showed significant postoperative morbidity (*Table 2*), there were no hospital deaths. Nine patients had an uneventful postoperative course. Among the other 11, eight developed one or more early complications within 30 days of operation. Serious problems requiring re-exploration in the immediate postoperative period occurred in four patients.

Small bowel obstruction and enterocutaneous fistula were the major complications most frequently encountered. Abscess formation in the abdominal wall or the perineum was another frequent problem. Two of three patients with small bowel complications in the early postoperative phase had a history of intensive radiotherapy to the pelvis. *Table 3* shows the rate of complications according to whether previous radiotherapy was given. The overall morbidity rate was substantially lower in the unirradiated group.

Enterocutaneous fistula occurred twice after standard total pelvic exenteration and once after the modified procedure.

In one very obese woman, necrosis of the ileal loop required reconstruction using an ileocaecal conduit. None of the patients with a sigmoid conduit developed small bowel problems.

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Table 2 *Postoperative complications*

Early complications (8 patients)	No.	Late complications (5 patients)	No.
Major		Major	
Small bowel ileus	3	Enterocutaneous fistula	1
Enterocutaneous fistula	2	Small bowel ileus	2
Urostomal necrosis	1	Paracolostomy hernia	1
Urinary infection	1	Pyelonephritis	1
Minor		Minor	
Abscess	3	Colostomy stenosis	1
Femoral vein thrombosis	1	Bacterial spondylitis	1
Femoral nerve impairment	2		
Depression	1		

Table 3 *Complications and previous irradiation*

	No problems	Major problems		Minor problems	
		Early	Late	Early	Late
Previous radiotherapy ($n = 13$)	5	3	4	5	1
No previous radiotherapy ($n = 7$)	4	1	0	2	0
Total ($n = 20$)	9	4	4	7	1

Late complications requiring readmission to hospital were observed in five patients. There were two stoma-related complications, a parastomal hernia and a colostomy stenosis in one patient each. Relaparotomy was required in three patients because of late small bowel obstruction, and in one patient nephrectomy was necessary for chronic pyelonephritis. One patient was treated for extensive bacterial spondylitis of L1–L4.

Follow-up was complete in all patients, with a range of 7–98 months. In 12 patients recurrent disease developed after a median of 8 (range 5–29) months. These recurrences were usually in the lung and liver. Pelvic recurrence was seen in only three patients after a mean follow-up of 19 months. Two of these patients, one with locally advanced recurrent rectal cancer and the other with recurrent carcinoma of the cervix, are still alive after 31 and 18 months respectively. The third patient had recurrent endometrial carcinoma and died 14 months after surgery.

The median overall survival period was 18 (range 7–98) months with a crude 2-year survival rate of 40 per cent. Ten patients died a mean of 12 months after operation (*Figure 1*). Eight patients are still alive without evidence of disease 17–98 (median 35) months after surgery. The median survival was 7 months after total pelvic exenteration when the lymph nodes were involved and 26 months in patients with histologically negative nodes. The survival time was similar in colorectal and gynaecological malignancy.

Of the nine patients with rectal cancer four, all with a primary advanced tumour, are free from recurrence a mean of 51 months after operation. Of these, three had Dukes' B_2 and one Dukes' C tumours. Of the five patients who underwent total pelvic exenteration for recurrence of Dukes' C rectal carcinoma (four) or locally advanced primary Dukes' C rectal cancer (one), four died with distant metastases without local recurrence a mean of 12 months after operation. One patient is alive 31 months after total pelvic exenteration with local pelvic recurrence combined with distant tumour.

Of the six patients with cancer of the cervix, three have no evidence of disease a mean of 50 months after operation. Two patients died with distant recurrence after 7 and 16 months, and one patient is alive with local recurrence 18 months after total pelvic exenteration.

Two patients with vaginal melanoma and one with vaginal carcinoma died from remote disease but without local recurrence at 7, 17 and 8 months respectively. The patient who has been treated for advanced bladder cancer is alive with no evidence of disease after 26 months.

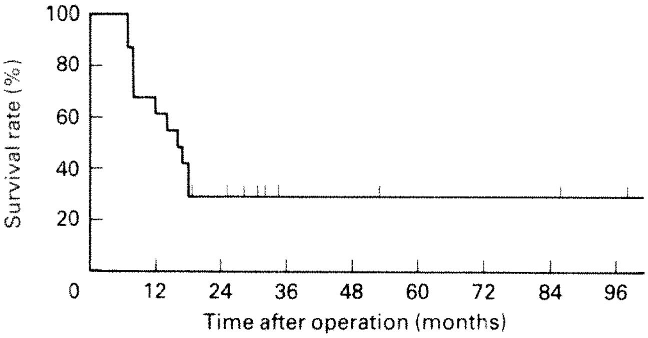

Figure 1 *Actuarial survival curve of all 20 patients undergoing total pelvic exenteration.* ⊥, *Survivors*

Discussion

Local pelvic recurrence can produce extremely distressing and usually disabling symptoms such as deep pelvic pain, urinary or faecal fistula and abscess. To improve quality of life in these patients by achieving local control, an extended surgical procedure such as total pelvic exenteration can sometimes be performed to resect the tumour along with invaded adjacent organs.

The first single-stage total pelvic exenteration was performed by Alexander Brunschwig in 1946. Later, he reported 22 patients of whom seven died in hospital[8]. Despite many improvements in operative and anaesthetic techniques and better preoperative and postoperative management, there is still a relatively high postoperative morbidity rate, whereas the reported mortality rate is about 5–10 per cent[11–13].

Candidates for pelvic exenteration should have no evidence of extrapelvic spread. Total pelvic exenteration is usually performed for the treatment of recurrent cervical and vaginal carcinoma. There is only a thin layer of loose connective tissue between the perirectal fat and the vaginal wall with its lymphatic connections[14]. Owing to the proximity of these organs and the trigone of the bladder, it is necessary to perform total pelvic exenteration for these locally advanced or early recurrent central pelvic tumours.

The 5-year survival rates in the literature in patients undergoing total pelvic exenteration range from 30 to 40 per cent[7]. The present results are consistent with this, with three of seven patients with cervical and vaginal carcinoma still alive with no evidence of recurrence a mean of 50 months after operation.

After resection of rectal cancer, local pelvic recurrence is also a significant problem. It is arguable whether total exenteration is suitable for local recurrence after abdominoperineal resection[2,15]. In many of these cases total pelvic exenteration has to be combined with sacral resection[16–19]. There is also some doubt about the applicability of the procedure to locally extensive primary colorectal carcinoma[5,15,20,21], but we believe that it should be considered in the absence of extrapelvic metastases. When there is tumour invasion in the trigone, at the ureterovesical junction or in the periprostatic region, total pelvic exenteration will offer the only possibility of local cure. Of the present four patients who underwent the procedure for recurrent rectal carcinoma, one developed local pelvic recurrence after 29 months. Distant metastases were observed in all of these patients after a mean of 8 months.

In the literature, there seems to be agreement that total pelvic exenteration should be reserved for patients younger than 70 years with biologically favourable malignant tumours. Suitable patients should not have demonstrable remote metastases or preoperative signs of invasion of the pelvic side wall such as sciatic nerve pain, venous obstruction of the legs with oedema and ureteric obstruction at the pelvic rim[3,4,22–27]. Patient factors such as general condition, obesity and concomitant disease also have to be taken into consideration.

At laparotomy, peritoneal carcinomatosis and extrapelvic visceral involvement have to be excluded. Better assessment of resectability can be made by bimanual palpation[28] and opening of the planes along the pelvic side walls between the bladder and the obturator fossa with frozen-section examination of any suspicious lymph node along the aorta and common iliac vessels. As the median survival was found to be very low for patients with histologically proven nodal metastases, it is now our policy to abandon total pelvic exenteration when para-aortic lymph nodes appear to be involved.

Most of the reported major complications requiring surgery are related to the small bowel, and occur in approximately 20–30 per cent of patients[12,15,29,30]. We have confirmed that the reported frequency is even higher after previous irradiation[29]. The majority of the early complications were intestinal obstruction, enterocutaneous fistula and inflammatory processes that developed within 3 weeks of surgery. These early complications are usually caused by technical failures or enteral anastomosis in a denuded part of the pelvis. Filling of the deperitonealized pelvic cavity with omentum or myocutaneous flap may prevent small bowel entrapment in this area at risk. Bricker[6,9] has suggested the use of a colonic conduit. Apart from avoiding a small bowel anastomosis, use of the colon provides a better external stoma with less chance of reflux at the ureterointestinal anastomosis. In this study we did not observe small bowel problems in any of the six patients with a ureterosigmoid conduit. Although the number of patients studied is relatively small, we recommend the use of a sigmoid conduit if it is oncologically justified and technically safe.

When it is oncologically sound, Hartmann's procedure should be performed by transecting the rectum at the level of the levator muscles[31]. By preserving the pelvic floor, this modification of the original total pelvic exenteration technique may also reduce complications.

In conclusion, total pelvic exenteration appears to be a relatively safe and effective option for an experienced team in the treatment of locally advanced pelvic malignancy. However, optimal criteria for patient selection are required because serious complications are common, affecting particularly the small bowel after previous irradiation. To reduce the risk of these complications, we recommend the use of Hartmann's procedure and a sigmoid urinary conduit if these modifications do not compromise the radicality of the resection.

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Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis

Twenty-four patients with familial adenomatous polyposis who had previously undergone prophylactic colectomy and had advanced duodenal polyposis were entered into a randomized trial to assess the effect of the non-steroidal anti-inflammatory drug sulindac on duodenal and rectal polyps. Polyp size and number were assessed by videotaped duodenoscopy (and rectoscopy in 14 patients) at entry and after 6 months of treatment; the tapes were compared by two assessors who were unaware of the randomization and the shuffled chronological order of the recordings. Mucosal cell proliferation was measured by in vitro *incorporation of 5-bromo-2′-deoxyuridine. Sulindac therapy was associated with a reduction in epithelial cell proliferation in the duodenum (median labelling index (LI) 15·8* versus *14·4 per cent, P = 0·003) and a trend towards duodenal polyp regression (P = 0·12). In the rectum, cell proliferation showed a marked reduction (median LI 8·5* versus *7·4 per cent, P = 0·018), and significant (P = 0·01) polyp regression was seen. Rectal polyposis was less severe than that in the duodenum and responded more dramatically. Sulindac is a possible treatment for patients in whom rectal polyps have failed to show significant regression after ileorectal anastomosis and who are unsuitable for pouch surgery; it may be useful in early duodenal polyposis or as an adjunct after duodenal clearance.*

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Duodenal adenomas are seen in 90 per cent of patients with familial adenomatous polyposis (FAP)[1]. Duodenal cancer is the leading cause of death in patients with FAP already treated by colectomy and ileorectal anastomosis[2], causing twice as many deaths as rectal cancer.

Treatment options for these duodenal polyps are limited. They cluster around the ampulla, are often sessile and recur after endoscopic or open surgical treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit experimental carcinogenesis[3,4] and their use in humans has been linked epidemiologically to a reduced risk of colorectal cancer[5]. There are a few reports[6,7] and two randomized trials[8,9] of the beneficial use of the NSAID sulindac in the treatment of patients with rectal polyposis.

The effect of sulindac on duodenal polyp regression, and rectal polyp regression where appropriate, was examined in a double-blind placebo-controlled trial in patients with advanced (Spigelman stage 3 or 4)[1] duodenal polyposis.

Patients and methods

Twenty-four patients (12 men; mean age 45 (range 27–70) years) with FAP and advanced duodenal polyposis (Spigelman stage 3 or 4)[1] were enrolled into the trial at least 5 years after colectomy. In 14 patients (eight men) who had undergone ileorectal anastomosis the rectum was also examined. Patients with a history of peptic ulcer disease or abnormal liver function were excluded.

Randomization was by sealed cards in blocks of six to receive either sulindac 200 mg twice a day (12 patients) or an identical-looking placebo (12). Sulindac and placebo were provided by Merck, Sharp and Dohme of Hoddesdon, Herts, UK. Videotaped duodenoscopy using an Olympus EVIS JFV10 side-viewing videoendoscope (Olympus, Keymed, Southend, UK) and, in 14 patients, videotaped rectoscopy using an Olympus EVIS CS100 endoscope were performed by the same endoscopist (C.B.W.) before and after 6 months of trial therapy. The endoscopist placed an opened biopsy forceps against any polyps to estimate their size. At the end of the study, paired videotapes from before and after treatment were viewed by two assessors (A.D.S., R.K.S.P.) who were unaware of their shuffled chronological sequence and the randomization. The second tape was recorded as 'better', 'worse' or 'no different' in comparison with the first. Only large changes in polyp status were accepted; any uncertainty resulted in a classification of 'no different'. Statistical analysis was by Fisher's exact test.

During each endoscopy, biopsies were taken from apparently normal mucosa for analysis of cell proliferation by *in vitro* incorporation of 5-bromo-2′-deoxyuridine (BrdU) by the method of Thornton *et al.*[10]. Biopsies were immediately orientated, under a microscope, in culture medium containing BrdU at a concentration of 500 μmol/l. They were placed in a sealed container infused with 95 per cent oxygen and 5 per cent carbon dioxide at 37°C for 1 h before fixation. All biopsies were examined histologically and crypts containing microadenomas excluded from the analysis. The mucosal proliferation rate was expressed as a labelling index (LI); the number of cells in the S phase of the cell cycle, which were labelled with BrdU, were divided by the total number of cells within a crypt. Twenty crypt columns were assessed for each patient at each time point. Statistical analysis to compare LIs before and after treatment with placebo or sulindac was by the Wilcoxon signed rank test.

Results

Duodenum

Endoscopic assessment. After sulindac treatment, polyp status improved in five patients, worsened in one and was unchanged in five. One patient taking sulindac stopped treatment within 6 weeks because of indigestion, although endoscopy did not reveal a duodenal ulcer or erosion. By contrast, after placebo therapy polyp status improved in only

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two patients, worsened in four and was unchanged in six ($P = 0{\cdot}12$). One patient in the control arm of the study developed duodenal cancer.

Cell proliferation. The mucosal BrdU LI fell by 10 per cent after sulindac treatment from a median value of 15·8 (range 14·1–19·8) per cent to 14·4 (range 12·2–15·9) per cent ($P = 0{\cdot}003$). By contrast, the median LI showed no change after placebo therapy, the pretreatment value being 14·9 (range 10·6–19·0) per cent and that after therapy 14·9 (range 11·1–22·1) per cent ($P = 0{\cdot}97$).

Rectum

Endoscopic assessment. After sulindac treatment, polyp status improved in five patients, worsened in none and was unchanged in two. By contrast, after placebo therapy no patients improved, two worsened and there was no change in five ($P = 0{\cdot}01$).

Cell proliferation. The LI fell by 11 per cent after sulindac treatment from a median of 8·5 (range 6·1–17·4) per cent to 7·4 (range 6·0–13·0) per cent ($P = 0{\cdot}02$). The index showed no significant change for patients receiving placebo, the median before therapy being 7·8 (range 6·7–9·1) per cent and that after 9·0 (range 6·9–9·5) per cent ($P = 0{\cdot}24$).

Discussion

This is the first study undertaken to evaluate the effect of sulindac on the duodenum of patients with FAP, although others[6,8] have used this drug to treat colorectal polyps. Patients with advanced duodenal disease were selected as there was an obvious clinical need to find an effective treatment for them and frequent endoscopic re-examination was clinically indicated. Indeed, one patient in the control arm of the study developed duodenal cancer in the interval between the first and second endoscopic assessments.

Sulindac treatment actively reduced mucosal proliferation in both the duodenum and rectum. Cell proliferation is a well validated marker of tumour formation in the gastrointestinal tract[11,12]. An increase in the cell proliferation rate has been shown to equate with a rise in the rate of tumour formation in the colon in both animal and human studies[13,14]. Therefore, a decrease in cell proliferation rate should precede a fall in the rate of tumour formation or a regression in the size and number of tumours present. The fall in mucosal proliferation in the present study was associated with significant polyp regression in the rectum. This is consistent with the findings of others.

Selection of patients with advanced duodenal disease meant that the study was small and lacked statistical power; this is perhaps why the improvement in duodenal polyp stage was not significant. Whereas duodenal polyposis was advanced in all cases, rectal polyposis was not and this might explain the lack of a statistically significant clinical effect in the duodenum. The effect of sulindac on polyps might be similar to that of calcium, where inhibition of cell proliferation is lost as polyps enlarge[15]. If this is so, sulindac may be of more benefit for patients with early duodenal polyps and as an adjunct to other therapy (endoscopic removal, where possible, or after duodenotomy) to prevent recurrence in those with advanced duodenal polyposis.

The mechanism for sulindac-induced inhibition of cell proliferation remains unknown. One hypothesis[9,16] is that, because sulindac inhibits the enzyme cyclo-oxygenase, there is a reduction in the concentration of prostaglandins E_2 and $F_{2\alpha}$. These prostaglandins are found in high concentrations in many tumours[17] and are thought to increase cell proliferation by raising the levels of adenosine 3′,5′-cyclic monophosphate and other intracellular second messengers of growth regulation[18] or by increasing angiogenesis within a tumour.

Finally, there are patients with uncontrollable rectal polyps, after ileorectal anastomosis, who are unsuitable or unwilling to undergo pouch surgery and in whom sulindac may be of benefit. In addition, some patients with intra-abdominal desmoid disease may have an irresectable colon and it would seem sensible to use sulindac in these to attempt to control the colonic polyposis. It must remain a future goal to manage FAP pharmacologically, without recourse to surgery, and also to apply this approach to patients with sporadic colorectal adenomas.

Acknowledgements

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Short note

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Pouch adenomas in patients with familial adenomatous polyposis

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Familial adenomatous polyposis (FAP) represents a human model of the adenoma–carcinoma sequence. Colectomy substantially reduces the cancer risk. Restorative proctocolectomy maintains continence and abolishes the risk of rectal cancer, but there is a price to pay in terms of an increased morbidity rate[1]. Long suture lines are prone to carcinogenesis experimentally, which raises concern that pouches might themselves be at risk[2].

To investigate this hypothesis, this study compared the incidence of ileal pouch adenoma with that of terminal ileal adenoma detected histologically after primary colonic surgery.

Patients and methods

To study adenomas in the ileal reservoir, 38 of 50 patients who underwent restorative proctocolectomy for FAP between 1977 and 1992 were followed by rigid sigmoidoscopy at 6 weeks, 3 months and subsequently yearly. All suspected adenomas were biopsied, the pathology being reviewed by one pathologist (I.C.T.).

To investigate adenomas in the intact terminal ileum, all pathology reports of colonic resection for FAP since 1918 were categorized into one of four groups: no record of ileal histology; normal ileum; lymphoid hyperplasia; and tubular adenoma.

Results

Adenoma in the ileal reservoir

The mean age of the 19 men and 19 women was 33 (range 15–57) years, with a mean follow-up of 4·7 (range 0·5–12·0) years. Mildly dysplastic tubular adenomas were found in seven patients at a median interval of 2 years (range 6 months to 7 years) from restorative proctocolectomy.

Four adenomas arose in ileal mucosa; one patient had single adenomas both in ileal and large bowel mucosa, and the other two had adenomas in large bowel mucosa and from no identifiable origin respectively. Thus five of the 38 patients developed true ileal adenomas at a median of 4 (range 1–7) years after pouch construction.

Ileal histology at initial colectomy was available for 27 patients: three had ileal adenomas, of whom one subsequently developed a pouch adenoma; five showed prominent lymphoid follicles only; and 19 were normal.

Adenoma in the intact terminal ileum

Between 1918 and 1992, 189 men and 127 women underwent primary colonic surgery for FAP with a mean age at operation of 28 (range 12–65) years. There was no record of ileal histology in 113. Of the remaining 203 patients, 143 were normal, 42 showed lymphoid hyperplasia and 18 (8·9 per cent) had ileal adenomas.

There was no significant difference between the proportion of ileal pouch adenomas and ileal adenomas at the time of colectomy (five of 38 *versus* 18 of 203; Yates' $\chi^2 = 0{\cdot}10$, 1 d.f., $P = 0{\cdot}75$).

Discussion

This study was not designed prospectively to detect the frequency of small pouch adenomas, which might be overlooked in an unprepared reservoir, but the findings are supported experimentally by the failure of carcinoma to develop preferentially in ileal pouches of mice given dimethylhydrazine[3]. Ileal carcinoma in FAP is rare, there being only five recorded cases in the literature[4,5]. It seems unlikely that ileal pouch carcinoma will be a problem in patients with FAP, but follow-up is short and cancer may still arise from retained large bowel mucosa.

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Secondary proctectomy and ileal pouch–anal anastomosis after ileorectal anastomosis for familial adenomatous polyposis

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Conversion of ileorectal anastomosis to ileal pouch–anal anastomosis (IPAA) was indicated in 29 patients with familial adenomatous polyposis but technically impossible in three because of unsuspected pelvic desmoid tumours. There was no operative mortality and overall postoperative morbidity and late complication rates were no different from those in a group of 120 patients who underwent IPAA as a first operative procedure. Unsuspected adenocarcinoma (one invasive, three in situ) *was found in four patients. The functional results in patients with IPAA did not differ from those of ileorectal anastomosis before conversion or from those obtained after IPAA as a first-choice procedure. Secondary proctectomy and IPAA can be safely offered to patients with ileorectal anastomosis and a high risk of rectal cancer.*

Familial adenomatous polyposis (FAP) is an inherited condition characterized by the development of at least 100 colorectal adenomas with an inevitable progression to carcinoma. The disease requires prophylactic treatment based on colectomy[1].

The development of restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) provides a treatment that eradicates all colorectal mucosa while preserving continence and ensuring good functional results[2]. IPAA is now established as the procedure of choice in patients with FAP presenting with numerous rectal polyps or in those unsuitable for follow-up[3].

Total colectomy with ileorectal anastomosis is still carried out in a number of centres since it provides more than acceptable prevention of colorectal cancer, it is easy to perform, it is associated with few complications and it gives good functional results[4,5]. Rectal excision following ileorectal anastomosis may be required for those with uncontrollable rectal polyposis or difficulty attending for regular follow-up. Conversion to IPAA, if possible, would represent an alternative to proctectomy with end ileostomy.

This study examined a series of patients with FAP who underwent conversion of ileorectal anastomosis into IPAA to determine the indications, feasibility, postoperative and late complications, and functional outcome. The results were compared with those from a larger group of patients undergoing IPAA as an initial surgical procedure.

Patients and methods

Between 1983 and 1991, 181 patients underwent surgery for FAP: IPAA, 148; ileorectal anastomosis, 21; proctocolectomy with ileostomy, eight; and laparotomy, four.

Conversion of ileorectal anastomosis to IPAA was indicated in 29 patients. These patients were reviewed with regard to the indication for secondary proctectomy, feasibility and technical difficulties, operative and pathological findings, mortality and morbidity, and functional results.

Operative procedure

During rectal dissection, care was taken to follow the muscular wall to avoid nerve damage, except in patients with rectal carcinoma in whom a large mesorectal excision was performed. Abdominal proctectomy left a short muscular cuff; a stapled J pouch was constructed and anastomosed manually to the dentate line following perineal mucosectomy[6]. A diverting loop ileostomy was performed and closed after 3 months, following pouchography.

Operative findings

Small bowel adhesions, perirectal sclerolipomatosis, mesenteric fibrosis and manoeuvres for mesenteric lengthening were noted.

Pathological findings

Preoperative rectal examination with multiple biopsy was performed and all proctectomy specimens reviewed by the same pathologist. Staging was based on Dukes'[7] classification.

Mortality and morbidity

Postoperative complications included all events occurring within 30 days of ileostomy closure and were classified according to treatment (medical or surgical). The length of hospitalization included the time for IPAA and ileostomy closure.

Bowel function

All patients undergoing IPAA were followed prospectively at 1, 3, 6 and 12 months and then annually, documenting daytime and night-time stool frequency, continence, ability to delay defaecation for more than 15 min, the need for a strict diet and the use of antidiarrhoeal medication. Incontinence was classified as none, minor (non-faecal staining of undergarments with fewer than three episodes per week) or gross (faecal staining with more than three episodes per week).

Comparison of data

Operative findings, mortality and morbidity, and the functional results at 1 year were compared with those obtained in a group of 120 patients who underwent IPAA for FAP as an initial surgical procedure. The functional results following conversion of ileorectal anastomosis to IPAA were compared with those obtained with ileorectal anastomosis before conversion in the same patients.

Statistical analysis

Comparisons between different groups were made using χ^2 analysis or Fisher's exact test as appropriate. $P < 0.05$ was considered significant.

Results

Indications for secondary proctectomy

Secondary proctectomy following ileorectal anastomosis was indicated in 29 patients. In 16 patients, rectal polyps were recurring in greater numbers at each successive examination. Eight patients wished to discontinue regular surveillance and proctectomy was required in three because of the discovery of rectal carcinoma (one Dukes' A tumour 3 years after ileorectal anastomosis, one Dukes' B 14 years after, one Dukes' C 17

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Table 1 *Intraoperative difficulties*

	IPAA after ileorectal anastomosis ($n = 26$)	IPAA initially ($n = 120$)	P*
Lysis of adhesions	11 (42)	4 (3)	<0·001
Proctectomy	9 (35)	3 (2)	<0·001
Mesenteric fibrosis	6 (23)	2 (2)	<0·001
Mesenteric lengthening	1 (4)	5 (4)	n.s.
Total no. of patients with difficulties	14 (54)	12 (10)	<0·001

Values in parentheses are percentages. IPAA, ileal pouch–anal anastomosis. *χ^2 test; n.s., not significant

Table 2 *Postoperative and late complications*

	IPAA after ileorectal anastomosis ($n = 26$)	IPAA initially ($n = 120$)
Postoperative complications		
Pelvic sepsis	1 (4)	1 (1)
Bowel obstruction	0 (0)	4 (3)
Miscellaneous	3 (12)	28 (23)
Late complications	4 (15)	18 (15)

Values in parentheses are percentages. IPAA, ileal pouch–anal anastomosis. There were no statistically significant differences

years after). Revisional surgery was indicated in two patients with a stricture producing poor functional results.

Feasibility

Proctectomy was impossible in three patients because of intra-abdominal desmoid tumours that had not been detected by preoperative ultrasonography and computed tomography. These patients refused end ileostomy and were left with ileorectal anastomosis with a large number of confluent rectal polyps. In the remaining 26 patients (14 male, 12 female), conversion to IPAA was performed a mean(s.d.) of 119(60) (range 4–276) months after ileorectal anastomosis, at a mean(s.d.) age of 35(12) (range 11–67) years.

Operative difficulties

Operative difficulties encountered were compared with those in the 120 patients who underwent IPAA as a first-choice procedure (*Table 1*).

Pathological findings

In addition to the three patients with known carcinoma, unsuspected neoplastic lesions were found in four other patients: one Dukes' A and three *in situ* tumours. All seven patients were alive without evidence of recurrence or metastatic disease after a mean follow-up of 54 months.

Mortality and morbidity

There was no operative mortality after conversion of ileorectal anastomosis to IPAA. Postoperative complications consisted of malaria crisis (one patient), pulmonary embolism (one), wound abscess (one) and pelvic sepsis requiring reoperation (one). Two patients had anastomotic stricture requiring dilatation under general anaesthesia, one had bowel obstruction and one developed an incisional hernia. There were no sexual or urinary problems. No patient developed a fistula and no pouch had to be removed. There was no increase in the rate of postoperative morbidity or late complication (*Table 2*).

Bowel function

Functional results were assessed in 23 patients (one was lost from follow-up after 6 months and two were excluded because they had a large mesorectal excision for known rectal carcinoma). The results are summarized in *Table 3* and compared with those for ileorectal anastomosis before conversion and for IPAA as a first surgical procedure in patients with FAP. During follow-up, two (8 per cent) abdominal desmoid tumours were diagnosed in the 26 patients undergoing conversion and seven (6 per cent) in the 120 who had IPAA without previous ileorectal anastomosis.

Table 3 *Bowel function*

	Ileorectal anastomosis before conversion ($n = 23$)	IPAA after ileorectal anastomosis ($n = 23$)	IPAA initially ($n = 120$)
Median (range) no. of stools per 24 h	3 (1–4)	4 (2–6)	4 (2–6)
Night-time evacuation*	3 (13)	10 (43)†	62 (52)
Normal daytime continence*	23 (100)	21 (91)	109 (91)
Normal night-time continence*	22 (96)	20 (87)	99 (82)
Can delay defaecation >15 min*	22 (96)	21 (91)	110 (92)
Antidiarrhoeal medication*	22 (96)	20 (87)	103 (86)
Avoids some foods*	23 (100)	21 (91)	98 (82)

*Values in parentheses are percentages. IPAA, ileal pouch–anal anastomosis. †$P = 0{\cdot}049$ (IPAA after ileorectal anastomosis *versus* ileorectal anastomosis before conversion, χ^2 test); there were no other statistically significant differences

Discussion

Since its introduction[8] for the treatment of patients with FAP, some centres have advocated restorative proctocolectomy as the procedure of choice while others have chosen a pouch procedure only when the risk of rectal cancer was perceived to be high: in dense rectal polyposis, colonic cancer and old age at operation or when poor follow-up was anticipated.

The cumulative risk of developing rectal carcinoma is age related and patients with an established ileorectal anastomosis need IPAA or more frequent rectal screening[9] after the age of 45 years. Patient desire to discontinue regular endoscopic examination, uncontrolled rectal polyposis, dysplasia or carcinoma in rectal adenoma, and poor outcome after ileorectal anastomosis are other reasons why reoperation is required.

Conversion to IPAA is not always feasible because of malignant disease or abdominal desmoid tumours. Desmoid tumours occur in 6·5–13 per cent of patients with FAP[10,11], mainly after previous surgery, and preoperative imaging techniques often fail to reveal these lesions. In the present series, the incidence of abdominal desmoid tumours found after conversion of the anastomosis did not differ from that after IPAA as a first surgical procedure. Desmoid tumours that developed after ileorectal anastomosis precluded secondary restorative proctectomy in 10 per cent of patients, and this may argue in favour of IPAA as the first surgical procedure.

Technical difficulties were significantly more frequent after secondary proctectomy than after initial IPAA but involved only the small bowel and rectal dissection. There were no difficulties in making the pouch or bringing it down to the anus. These difficulties did not prevent the formation of an IPAA and were not responsible for increased numbers of complications.

The finding of four previously unsuspected rectal neoplasms underlines the difficulties in surveillance. A careful and regular rectal examination every 6 months with systematic destruction of all newly found polyps does not preclude the onset of rectal cancer. Others[9] have documented cancer of the rectum developing in 22 of 224 patients with ileorectal anastomosis, in 14 despite careful 6-monthly follow-up. Nine of the tumours were Dukes' C lesions when discovered. There may be a need to change the frequency of screening and to propose rectal excision as soon as moderate or severe dysplasia is found.

The functional results of secondary IPAA differ slightly from those of ileorectal anastomosis before conversion, and other studies[12,13] have shown that ileorectal anastomosis and IPAA produce similar results. In a previous study[14] it was shown that after conversion of ileorectal anastomosis to IPAA 90 per cent of patients felt that bowel function was unchanged or improved.

Bowel function following conversion of ileorectal anastomosis did not differ from that following IPAA as a first operative procedure. This differs in patients with ulcerative colitis, in whom poor results occur after conversion of ileorectal anastomosis into IPAA[15]. This is probably explained by the lack of subsequent rectal inflammation in those with FAP.

In patients with a high risk of rectal cancer, ileorectal anastomosis should be readily converted to IPAA. The postoperative complication rate and the functional results do not differ from those observed after IPAA as a primary procedure, and proctectomy may reveal unsuspected rectal carcinoma.

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SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, December, 1624–1625

A selection from the November issue of the American journal.

Shear stress increases the release of interleukin-1 and interleukin-6 by aortic endothelial cells

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Background. *The aim of this study was to determine the correlation between shear stress and the release of interleukin-1 (IL-1) and interleukin-6 (IL-6) by endothelial cells (EC).*

Methods. *Bovine aortic EC were seeded in fibronectin-coated cylinders at 1.0 × 10^6 cells/tube and allowed to reach confluence and to adhere for 48 hours. The experimental groups were subjected to a laminar flow of 100 ml/min (6 dyne/cm^2). The control group was subjected to similar incubation conditions without flow. The release of IL-1 and IL-6 by EC was measured by enzyme-linked immunosorbent assay.*

Results. *Shear stress increased significantly ($p < 0.01$) the release of IL-1 and IL-6 by EC. The release of these two cytokines had different kinetics.*

Conclusions. *Increasing shear stress facilitates release of IL-1 and IL-6 by EC. Previous reports have shown that IL-1 and IL-6 promote vascular smooth-muscle cell proliferation. Thus abnormal flow conditions with increasing shear stress may predispose to smooth-muscle cell proliferation that characterizes early atherosclerotic plaque development by an interleukin-mediated mechanism. (*SURGERY *1993;114:911-4.)*

Tyrosine inhibits intestinal-phase gastric-acid secretion

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Background. *Intestinal infusion of leucine augments the maximal gastric-acid secretory response to pentagastrin and serves as a bioassay for intestinal-phase acid secretion. Another action of leucine is to decrease tyrosine flux into neural tissues. We hypothesized that the mechanism of leucine-stimulated acid secretion involves its ability to alter tyrosine absorption.*

Methods. *We administered tyrosine intrajejunally and intravenously to anesthetized, vagotomized rats during maximal pentagastrin stimulation and measured acid output in response to intrajejunal infusion of leucine.*

Results. *Intrajejunal tyrosine produced a dose-dependent inhibition of leucine-stimulated acid secretion but only mild effects on acid secretion in response to pentagastrin alone. Intravenous tyrosine infusions also decreased acid secretion in response to intestinal leucine but required much higher doses.*

Conclusions. *Tyrosine exerts a specific inhibitory effect on leucine-stimulated acid secretion, which is mediated intraluminally. Because tyrosine is an important regulator of adrenergic nervous system activity, we speculate that the mechanism of leucine-stimulated acid secretion may involve modulation of the sympathetic nervous system, thereby affecting acid secretion. (*SURGERY *1993;114:915-20.)*

Characterization of cholecystokinin receptors on the human sphincter of Oddi

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Background. *The present in vitro study investigated the interaction between cholecystokinin (CCK) and receptors on human sphincter of Oddi tissue obtained from donated human livers that were being transplanted.*

Methods. *Radiolabeled ligands with cholecystokinin receptor specificity, autoradiography, and crystal scintillation counting were used to directly characterize cholecystokinin receptors on tissue sections.*

Results. *The binding of ^{125}I-BH-CCK-8 to the tissue was saturable, specific, and dependent on time, pH, and temperature. Saturable binding of ^{125}I-BH-CCK-8 was localized on the smooth muscle layer, and binding was inhibited only by cholecystokinin-related peptides. Computer analysis of ^{125}I-BH-CCK-8 binding indicated the presence of two classes of binding sites, one with a high affinity and the other with a low affinity for CCK-8. CCK-8 caused relaxation (half-maximal concentration, 6 nmol/L) and carbachol caused contraction (half-maximal concentration, 10 nmol/L) of circular, cross-sectional strips of the tissue. Longitudinal strips were less responsive. The relative ^{125}I-BH-CCK-8 binding inhibition potency of CCK-8 agreed closely with its relative ability to cause sphincter relaxation. Tetrodotoxin (1 μmol/L) and atropine (1 μmol/L) caused a rightward shift of the dose-response curve for CCK-8-stimulated sphincter relaxation.*

Conclusions. *The present results indicate that cholecystokinin receptors on the human sphincter of Oddi are sulfate dependent and mediate sphincter relaxation. (*SURGERY *1993;114:942-50.)*

Nitric oxide–mediated, endothelium-dependent vasodilation is selectively attenuated in the postischemic extremity

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Background. *Attenuation of endothelium-dependent relaxing factor (EDRF) release may contribute to adverse sequelae commonly seen after reperfusion of an acutely ischemic* *extremity. The purpose of this study was to identify the compound responsible for the EDRF activity in the extremity and to evaluate its modulation by ischemia and reperfusion.*

Methods. *Isolated rat hindlimbs were perfused at constant pressure with an albumin-enriched crystalloid buffer. Increasing log dose infusions of acetylcholine and nitroprusside were used to measure endothelium-dependent (EDRF-mediated) and endothelium-independent vasoreactivity, respectively.*

Results. *Graded reductions in total vascular resistance were seen in response to both agonists in the control group ($n = 11$). In the postischemic group ($n = 7$), 60 minutes of normothermic ischemia and 10 minutes of reperfusion reduced endothelium-dependent vasodilation to acetylcholine by approximately 40% ($p < 0.01$). Endothelium-independent vasodilation to nitroprusside was unaffected. N^G-monomethyl-L-arginine (L-NMMA), a competitive inhibitor of nitric oxide release, attenuated vasodilation to acetylcholine ($p < 0.01$) but not nitroprusside in both control and postischemic groups.*

Conclusions. *Endothelium-dependent vasodilation in the rat hindlimb, mediated by nitric oxide, was selectively impaired by injury from ischemia and reperfusion. Strategies designed to minimize postischemic attenuation of nitric oxide release may be beneficial in the management of acute limb ischemia. (SURGERY 1993;114:960-7.)*

Clinical significance of routine imaging of iliac and calf veins by color flow duplex scanning in patients suspected of having acute lower extremity deep venous thrombosis

Louis M. Messina, MD, Mary S. Sarpa, MS, RVT, Mary A. Smith, RVT, *and* **Lazar J. Greenfield, MD,** *Ann Arbor, Mich.*

Background. *Because duplex ultrasonography is used increasingly to evaluate patients suspected of having acute deep venous thrombosis of the lower extremity, the clinical significance of limiting venous duplex scanning to the common femoral, superficial femoral, and popliteal veins becomes an important question.*

Methods. *We prospectively studied by venous color flow duplex ultrasonography 181 patients referred for evaluation to rule out acute deep venous thrombosis in determine (1) the frequency with which the iliac and calf veins could be imaged adequately to determine the presence or absence of acute deep venous thrombosis, (2) the frequency of acute venous thrombosis in these venous segments, and (3) the time required to scan these additional segments.*

Results. *In 79% of the patients studied, one segment of the iliac venous system was imaged adequately to determine the presence or absence of venous thrombosis. In the lower extremity, the common femoral vein, the superficial femoral vein, and the popliteal vein were imaged adequately in 94% of the patients. In 76% of the patients all three calf veins were imaged adequately to determine whether acute deep venous thrombosis was present or absent. The anterior tibial vein was the most difficult vein to image consistently and was imaged adequately in 76% of the patients referred. The mean time to scan the affected limb was 8 minutes 37 seconds. Forty-seven patients (26%) of the 180 patients studied had positive venous scans. Twenty-three percent of the patients who had positive scans were found to have iliac vein involvement. Thirty-two percent who had positive venous scans were found to have thrombosis of the calf veins. Fifteen percent of the 47 patients who had positive scans had either an isolated iliac or calf vein thrombosis.*

Conclusions. *We believe this frequency of isolated iliac or calf vein thrombosis coupled with the frequency of successful imaging of these venous segments and the short additional time required to image these segments justifies the inclusion of routine imaging of the iliac and calf veins in patients undergoing venous duplex scanning to rule out acute deep venous thrombosis. (SURGERY 1993;114:921-7.)*

Technical considerations and complications associated with the placement of 180 implantable hepatic arterial infusion devices

Steven A. Curley, MD, Judy L. Chase, PharmD, Mark S. Roh, MD, *and* **David C. Hohn, MD,** *Houston, Texas*

Background. *Treatment regimens with hepatic arterial chemotherapy infusion are being investigated in an attempt to improve survival and quality of life for patients with primary and metastatic liver malignancies. The successful delivery of chemotherapeutic drugs through an implantable hepatic arterial infusion device depends on the surgeon's understanding of hepatic arterial anatomy, the proper cannulation technique, and the operative measures necessary to prevent misperfusion of drug.*

Methods. *Between January 1, 1987, and December 31, 1991, we placed implantable hepatic arterial infusion devices in 180 patients. The records of these patients were reviewed to determine (1) the incidence and surgical management of variant hepatic arterial anatomy and (2) the complications associated with surgical placement of these devices.*

Results. *Variant hepatic arterial anatomy requiring ligation of the variant vessel or nonstandard cannulation was seen in 66 patients (36.7%). Treatment response rates and duration of treatment were no different for these 66 patients than for the 114 patients with standard hepatic arterial anatomy ($p = 0.94$). There were no operative deaths in this series. Operative or early postoperative (within 30 days) complications occurred in 10 patients (5.5%). However, late complications or device-related malfunctions developed in 52 patients (28.8%).*

Conclusions. *An understanding of regional arterial anatomy is required to surgically place a catheter to achieve bilobar hepatic arterial perfusion and avoid gastroduodenal misperfusion of drug. Placement of hepatic arterial infusion devices has a low rate of early morbidity, but surgeons should be aware of late complications that may develop in patients undergoing hepatic arterial chemotherapy infusion through an implantable device. (SURGERY 1993;114:928-35.)*

Correspondence

Oesophagogastric intramural implantation anastomosis after oesophagectomy

Sir
I found the Surgical Workshop by Dr Cheng and colleagues (*Br J Surg* 1992; **79**: 1325–6) quite enlightening. The authors' ingenuity in creating the flap-valve effect prevents reflux and so ultimately oesophagitis. The risk of stricture as a complication is thus kept to a minimum.

The same principle of a flap-valve was reported by Stepanov[1] in children who had undergone resection of the ileocaecal junction for various lesions in this area, with subsequent ileocolic anastomosis. The method prevents reflux of colonic material into the ileum, forcing passage of intestinal contents in a unilateral direction. Our initial unpublished experimental studies on rats gave satisfactory results, and the method was subsequently introduced into paediatric clinical surgery. Complications are similar to those highlighted by Cheng and colleagues, namely stricture (stenosis), and are caused by oversewing, crushing by the clamp, poor apposition and local infection.

This method should find wide application when resecting lesions in the ileocaecal region.

A. Archibong

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Nigeria

1. Stepanov AE. Ileo-caecal resection with ileo-colic anastomosis in children. *Thesis in Paediatric Surgery*. Moscow: Supreme Attestation Commission, 1991.

Sutureless circumcision

Sir
I am surprised that the Journal (*Br J Surg* 1993; **80**: 859) allows such an inaccurate anatomical term as 'mucocutaneous approximation'. When I studied anatomy the glans penis was covered with skin, and I doubt that it has changed.

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Non-therapeutic operations for penetrating trauma: early morbidity and mortality

Sir
We were interested to read the findings of Professor Demetriades and colleagues (*Br J Surg* 1993; **80**: 860–1) regarding the complications of non-therapeutic surgical intervention for penetrating trauma. We make the following comments.

First, we would question the implication that a negative operation, as defined by them, adds little to management. Negative findings can contribute importantly to overall management of the patient.

Second, we are confused by the authors' concluding paragraph about their selective conservative policy. The study did not investigate this policy, and the authors did not state whether such a policy was in force during the study. In any case an appreciable number of non-therapeutic procedures (12 per cent) were performed.

Finally, it would be nice to know the complication rate in patients with penetrating injuries who were not operated on during the study period, and how many of these came to operation later. This information should be available if the study was prospectively conducted.

Penetrating injuries sufficient to warrant surgery are far less common in the UK than in South Africa. There can be few hospitals here that undertake annually almost 300 abdominal or thoracic explorations for trauma. This fact, combined with the organization of UK trauma services, means that one would expect the non-therapeutic operation rate here to be much higher. Knowledge of the attendant complication rate is salutary and represents another argument for greater concentration of trauma services within the UK.

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Authors' reply

Sir
We would like to thank Messrs Saha and Scriven for their comments on our paper. We did not imply that a negative operation adds little to management. We wrote that non-therapeutic operations may be associated with important risks and that these should be avoided whenever possible. Clinical examination is reliable in detecting serious injuries, and a selective conservative policy is recommended. This policy is supported by previous studies from our institution[1–3]. In the present publication we did not study the complications in patients treated non-operatively. However, we looked into this matter in three previous prospective studies[1–3]. The complication rate in patients treated conservatively was low (less than 1 per cent) and, most importantly, there were no deaths.

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1. Demetriades D, Rabinowitz B. Indications for operation in abdominal stab wounds. A prospective study of 651 patients. *Ann Surg* 1987; **205**: 129–32.
2. Demetriades D, Rabinowitz B, Sofianos C *et al.* The management of penetrating injuries of the back. A prospective study of 230 patients. *Ann Surg* 1988; **207**: 72–4.
3. Demetriades D, Charalambides D, Lakhoo M, Pantanowitz D. Gunshot wounds of the abdomen: role of selective conservative management. *Br J Surg* 1991; **78**: 220–2.

Anal fistula

Sir
The Review by Messrs Seow-Choen and Nicholls (*Br J Surg* 1992; **79**: 197–205) acknowledges that hydrogen peroxide may be of use in locating the internal openings of anal fistulas and refers to reports of possible dangers. They mention other more frequently used agents in the same breath, but rightly only to condemn.

It would be regrettable if the impression were conveyed that hydrogen peroxide is in the same category as the other agents. Hydrogen peroxide has provided instant recognition of all chronic fistulas in which it has been used. More importantly, it has differentiated between fistulous and non-fistulous acute abscesses in almost all, if not all, instances and eliminated exploratory probing, its attendant ills and subsequent examination under anaesthesia. If the abscess is of fistulous origin, the involved anal gland is also indicated.

Designation of the concentration of hydrogen peroxide as 3 per cent, while possibly more scientific, does not alert the unwary to the evolution of ten volumes of oxygen per unit volume, as the older '10-volume' designation emphasizes. It is essential for this reason to use a *small volume*, as advised[1]. In neither of the cases quoted by Beavis[2] was hydrogen peroxide used as advised. Even safe materials require to be used with due respect for their properties.

> 'For when the groaning girder lets down the sagging span the fault lies not with the metal, the fault lies with the man'

... or words to that effect.

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1. Glen DL. Use of hydrogen peroxide to identify the internal opening of anal fistula and perianal abscess. *Aust N Z J Surg* 1986; **56**: 433–5.
2. Beavis RE. Use of hydrogen peroxide to identify the internal opening of anal fistula and perianal abscess. *Aust N Z J Surg* 1987; **57**: 137 (Letter).

Authors' reply

Sir

Contrary to what Dr Glen would have us believe, hydrogen peroxide is indeed in the same category as the other agents mentioned in our Review. Hydrogen peroxide has its place in surgery, but it has its dangers as well. It may be more useful than methylene blue or saline in the assessment of internal openings of anal fistula, but its potential dangers are greater than those of these other agents.

I have found exploratory probes to be of immense value and without attendant ills so far in my practice, and I use them routinely in the surgery of anal fistula and abscess[1]. No doubt the probe is dangerous if due respect is not accorded. As Dr Glen would say: 'The fault lies not with the metal, the fault lies with the man'.

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1. Seow-Choen F, Leong AFPK, Goh HS. Results of a policy of selective fistulotomy for primary anal abscess. *Aust N Z J Surg* 1993; **63**: 485–9.

Diaphragm-like strictures of the colon induced by non-steroidal anti-inflammatory drugs

Sir

Mr Pucius and colleagues (*Br J Surg* 1993; **80**: 395–6) published a Case Report on diaphragms in the caecum and strictures in the ascending colon, claiming that this was 'the first description of a patient with (such) strictures in the colon'. We draw their attention to a previous paper[1] in which we carefully stated that 'to our knowledge such a case has not been observed before'. Our caution was justified because we learned that earlier publications of two such cases had appeared[2] in 1989, and this condition has also been reported in endoscopic studies[3] and elsewhere[4,5].

We fully agree with an editorial stating that colonic damage by non-steroidal anti-inflammatory drugs (NSAIDs) is probably very common[6]. We recently published a more extended report including seven patients seen in our departments who were treated with diclofenac in slow-release form[7]. It is possible that we saw all such cases in the past 10 years as this drug is manufactured in Switzerland and is the most commonly used NSAID in our country.

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1. Huber Th, Ruchti Ch, Halter F. Non-steroidal anti-inflammatory drug induced colonic strictures: a case report. *Gastroenterology* 1991; **100**: 1119–22.
2. Sheers R, Williams WR. NSAIDs and gut damage. *Lancet* 1989; **ii**: 1154.
3. Monahan W, Starnes EC, Parker AL. Colonic strictures in a patient on long-term non-steroidal anti-inflammatory drug. *Gastrointest Endosc* 1992; **38**: 385–6.
4. Fellows JW, Clarke JMF, Roberts PF. Non-steroidal anti-inflammatory drug-induced jejunal and colonic diaphragm disease. *Gut* 1992; **33**: 1424–6.
5. Halter F, Huber Th, Ruchti Ch. Non-steroidal anti-inflammatory drug induced jejunal and colonic diaphragm disease. *Gut* 1993; **34**: 715.
6. Editorial. NSAIDs and gut damage. *Lancet* 1989; **ii**: 600.
7. Halter F, Weber B, Huber Th, Eigenmann F, Frey M, Ruchti Ch. Diaphragm disease of the ascending colon associated with sustained-release diclofenac. *J Clin Gastroenterol* 1993; **16**: 74–80.

Cytodiagnosis of breast disease using a liquid suspension medium

Sir

Although Mr Ross and colleagues (*Br J Surg* 1993; **80**: 866–7) indicate that preparing slides from a fine-needle aspirate taken from a breast mass is highly operator dependent, they fail to mention that the technique of needle aspiration of breast lumps is likewise operator dependent[1–3]. When cytology is performed by experienced aspirators the results obtained are better than those reported by Ross and colleagues[1,3–5]. Surely it would be more sensible to ensure that fine-needle aspiration cytology is performed by experienced aspirators who have learned how to prepare their own slides rather than to allow inexperienced surgeons to perform fine-needle aspiration and thereafter to use a liquid suspension medium.

J. M. Dixon

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1. Dixon JM, Lamb J, Anderson TJ. The importance of the aspirator. *Lancet* 1983; **ii**: 564.
2. Barrows GM, Anderson TJ, Lamb J, Dixon JM. Fine needle aspiration of breast cancer: relationship of clinical factors to cytology results in 689 primary malignancies. *Cancer* 1986; **58**: 1493–8.
3. Ciatto S, Cariaggi P, Bulgaresi P, Confortini M, Bonardi R. Fine needle aspiration cytology of the breast: review of 9533 consecutive cases. *Breast* 1993; **2**: 87–90.
4. Dixon JM, Anderson TJ, Lamb J, Nixon SJ, Forrest APM. Fine needle aspiration cytology in relationship to clinical examination and mammography in the diagnosis of a solid breast mass. *Br J Surg* 1984; **71**: 593–6.
5. Dixon JM, Clarke PJ, Crucioli V, Dehn TCB, Lee ECG, Greenall MJ. Reduction in the biopsy rate in benign breast disease using fine needle aspiration cytology with immediate reporting. *Br J Surg* 1987; **74**: 1014–16.

Authors' reply

Sir

Thank you for the opportunity to reply to the comments of Mr Dixon. We agree that fine-needle aspiration biopsy is highly operator dependent. We stressed this point in the first paragraph of our Introduction and again early in the Discussion. We further concur with his sentiments that more experienced clinicians would be desirable, but this is an uncommon luxury outside teaching hospitals. Like so much in surgical practice, the performance and results of fine-needle aspiration biopsy will be optimized by experience, and it was neither stated nor implied that the Cytospin method (Shandon Scientific, Runcorn, UK) compensated for a lack of such experience.

The central tenet of this paper is that the Cytospin technique provides an inherently simple and flexible method of processing fine-needle aspiration biopsy samples. It may have additional benefits in terms of resource allocation and infection control. It has proved to be as diagnostically accurate as conventional cytology in our unit and in larger series also quoted in our paper.

D. A. Ross

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Mechanical properties of the aneurysmal aorta

Sir

I am grateful to Mr MacSweeney and Dr Powell for their reply (*Br J Surg* 1993; **80**: 672) to my letter regarding the article by themselves and others (*Br J Surg* 1992; **79**: 1281–4). I am surprised to find myself accused of thinking that the aortic wall exhibits simple elastic mechanical properties when I stated the contrary in the final paragraph of my letter; my only mention of the aorta behaving as a simple elastic structure is written in the subjunctive ('if we imagined ...').

This hypothetical proposition is, however, necessary to permit a mathematical understanding of the effect that Laplace's law will tend to exert on the pressure–strain elastic modulus. The fact that increasing stiffness with distension of the vessel exerts an opposite effect on this modulus does not allow one to disregard the effect of Laplace's law, still less to suggest that the law itself determines this opposite effect.

Far from being irrelevant, appreciation of this fact is crucial if conclusions regarding the behaviour and structure of the aorta are to be drawn from various values of the pressure–strain elastic modulus. The actual stress on the vessel wall varies not just with pressure, but also with the diameter and thickness of the wall; it can be estimated only with a correct understanding of Laplace's law.

I took issue with the statements following and in the same paragraph as the introduction of Laplace's law. These appeared to be discussing the effects of the law. If the intention was simply to reiterate the undisputed fact that the wall becomes stiffer as it is stretched, there would seem little point in mentioning Laplace's law. This law determines tension, i.e. the force that tries to overcome the increasing stiffness of the wall. Of course, tension is required to stretch any structure, but the change in resistance offered by the stretched vessel wall is the result of elongation rather than tension *per se*. At any moment, tension acts in one direction and the resistance of the vessel wall in the opposite direction.

Their defence of the extraordinary statement that increased wall tension 'would resist further distension' reminds me of a small boy sitting opposite a fat man on a see-saw and complaining that gravity is lifting him up in the air! Such a statement is as true as it is untrue as it is ambiguous.

F. L. Hinson

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Authors' reply

Sir

Mr Hinson has provided us with another opportunity to reiterate the dependence of the mechanical properties of the aorta on the composition and microanatomy of this vessel.

In the normal young aorta the principal load bearing is attributable to the elastic fibres but, as the aorta ages and distends, the much stiffer collagen fibres are recruited to aid in load bearing. In our paper, comment concerning Laplace's law was introduced at the request of peer review. Mr Hinson appears to have misunderstood us to imply that Laplace's law is the cause of the non-linear properties of the aorta; of course it is not. The structure of the arterial wall determines its mechanical properties. We believe this to be clear from attentive reading of our paper. We have already commented about 'resisting further distension' in our previous correspondence. However, we are in agreement in the direction in which the see-saw would move.

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J. T. Powell

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Superselective intra-arterial chemotherapy with mitomycin for gallbladder cancer

Sir

We read with interest the article by Drs Mäkelä and Kairaluoma (*Br J Surg* 1993; **80**: 912–15) on regional chemotherapy in the treatment of gallbladder cancer. The authors state that superselective intra-arterial chemotherapy with mitomycin can be useful for patients with cancer restricted to the gallbladder wall and cite the successful result of mitomycin used intra-arterially in advanced gallbladder cancer by von Eyben *et al.*[1]. Although gallbladder cancer is thought to be resistant to chemotherapy, the sensitivity rate to mitomycin and cisplatin were 75 and 60 per cent respectively in our series (*Table 1*).

Table 1 *Sensitivity to anticancer drugs in carcinoma of the gallbladder*

	Sensitivity
Mitomycin	3 of 4
Cisplatin	3 of 5
Carboquone	2 of 5
Doxorubicin	1 of 5

Sensitivity was evaluated as a reduction in succinate dehydrogenase activity to less than 50 per cent of the untreated control value

This fact must surely reflect the potential advantage of regional chemotherapy in the treatment of gallbladder cancer.

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1. von Eyben E, Hellekant C, Mattsson W, Ljungvist U, Jonsson K. Mitomycin C in advanced gallbladder carcinoma. *Acta Radiol* 1980; **19**: 81–4.

Book reviews

Minimally Invasive Therapy in Five European Countries

H. D. Banta (ed.). 270 × 195 mm. Pp. 177. Not illustrated. 1993. Amsterdam: Elsevier Science Publishers. US $212·50.

This book could not be more timely because of the rapid changes occurring in surgical management, with the introduction of minimally invasive therapy across a range of specialties. There is also current disquiet in the medical literature as well as in the media about isolated anecdotal evidence of adverse effects of new treatments. The book contains an excellent introduction by Mr J. Wickham, well known for his pioneering efforts both in clinical applications and in bringing the changes consequent upon new treatments to the attention of a wider audience. The other contributions are all from various health economists in the European countries studied.

The disadvantage of this book is that there is no contribution from a practising clinician (other than that from Mr Wickham in the Introduction) experienced in any of the new therapies discussed. Specialist societies for minimally invasive therapy and specialist journals are now well established; it would surely have been sensible to have included comments from leading clinicians in some of the areas studied. This omission leads inevitably to the book failing to cover some of the problems raised by the rapid rate of progress. There is no discussion of the problem of necessary changes in surgical training. Some of the examples chosen for study, such as the treatment of bladder tumours by laser, are at such an early stage that it is difficult to see why they were included. Other obvious examples of dramatic but long-standing change (briefly mentioned by Mr Wickham), such as the replacement of open bile duct surgery by endoscopic treatment, are not considered at all.

Several contributors make the point that more studies of clinical efficacy and cost–effectiveness are needed, and that knowledge of the results needs to be disseminated widely to doctors so that appropriate referral decisions can be made. The coordinating author in his final contribution states that 'few organisations are actively involved in evaluations to affect clinical practice'. This is an extraordinary statement in the light of efforts made by many specialist societies to study, discuss and criticize new minimally invasive techniques. However, the policy changes suggested do seem sensible. Indeed, these are already being addressed in the UK by the formation of centres across the country for specialized training in minimally invasive therapy with the help of the Wolfson Foundation.

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ABC of Colorectal Diseases

D. J. Jones and M. H. Irving (eds). 295 × 210 mm. Pp. 103. Illustrated. 1993. London: BMA. £12·95.

This book is based on the popular *ABC* series of articles published in the *British Medical Journal* last year. Revised and updated, it provides an overview on diseases of the colon and rectum, with chapters on trauma, tropical and sexually transmitted diseases, and paediatric problems. The authors are to be congratulated on their clear style, the simple and easy to read English and the informative tables and illustrations used, making this book essential reading for students, and physicians and surgeons in training. It would be especially valuable as a quick revision aid to those about to sit the Part II FRCS examination. Frankly, there is little to criticize in this excellent book, which contains up to date information on management policies, practical hints that would be useful in everyday clinical life as well as several 'tricks of the trade'. However, I was somewhat disappointed to see that some chapters, such as that on faecal incontinence, do not receive the detailed attention they deserve. All in all, I found the book very enjoyable to read and thoroughly recommend it.

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Microvascular Surgery of the Extremities

Zhongjia Yu (ed.). 240 × 155 mm. Pp. 521. Illustrated. 1993. Heidelberg: Springer. DM 398.

This book appears to be the natural successor to *Microsurgery*[1]. The present editor, Dr Zhongjia Yu, has succeeded Dr Chen Zhong-Wei as chief of the orthopaedic department in the Shanghai Sixth People's Hospital. The scope of microsurgery in this book is restricted to upper- and lower-limb reconstruction, of which Dr Yu has experience of hundreds of cases. The depth of this experience is reflected in examples of reconstruction of many rare traumatic conditions, such as reconstruction of the digitless hand. There is a fascinating description of the techniques, which Dr Yu has pioneered, of metacarpal reconstruction with a two- or three-pronged endoprosthesis. The proximal single stem is inset into the fenestrated radial medullary cavity, while either single- or double-toe transplants are attached to the distal prongs, giving functional pinch or key grip depending on the number of digits used.

The book is well set out with accurate and informative chapters on basic anatomy and transplant dissection techniques, and large sections on thumb and hand reconstruction. There is a generous section on cross-leg free flaps, used when the vessels in the damaged limb are unsuitable for anastomosis; anastomosis is carried out on the opposite undamaged limb (so-called cross-bridge procedure).

The quality of photographs, illustrations and printing is excellent and although some of the reconstructive procedures may not be acceptable to Western patients this book is, I believe, something that every plastic or orthopaedic reconstructive surgeon carrying out microsurgical repair would like to own.

P. L. G. Townsend

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1. Chen Zhong-Wei, Yong Dong-Yu, Chong Di-Sheng. *Microsurgery*. Heidelberg: Springer, 1982.

Surgical Decision Making

F. T. de Dombal. 215 × 136 mm. Pp. 157. Illustrated. 1993. Oxford: Butterworth–Heinemann. £14·95.

It is a pity that the habit of giving subtitles to books seems to find less favour than it did in Victorian times. A first-class subtitle to de Dombal's book would be: 'Letters to a young surgeon concerning some of the things that you were not taught at medical school'. The author tries to make the young surgeon think. Doctors, he writes, must first of all acquire information from patients – by taking a history and doing a physical examination. They must analyse this information and make a decision about management: What special tests are needed? What intervention is appropriate? There is an interesting chapter on the development of Bayes' theorem, particularly in relation to abdominal pain; de Dombal stresses its application to surgical decision making. One starts with a prior probability that more people with new pain in the right lower abdomen have appendicitis than any other single disease, for example. One then reaches a conditional probability as more information is gathered and, ultimately, a final probability (but never a certainty) on which to act. At the same time the utility of opposing decisions is judged and the course that promises the most utility chosen.

The author is at pains to draw a distinction between making a diagnosis and making a decision, and this is one of the strengths of the book. There is practically no mention of computer-assisted decision making and none of the equations that would only confuse non-mathematical surgeons. This is a book that I would like to think will be read and enjoyed by every new surgical house officer. I also hope that senior people will take in the message and pass it on to their trainees.

A. V. Pollock

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Notices and announcements

6–7 January 1994
Surgical Research Society Meeting
London, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

31 January to 4 February 1994
Pan-Pacific Surgical Association 22nd Congress
Hong Kong
Information: Congress Secretariat, PPSA Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

9–12 February 1994
5th International Steglitz Symposium – Sepsis
Berlin, Germany
Information: Mrs Lynn Hazlewood, Department of Anaesthesia and Operative Intensive Care, Klinikum Steglitz, Hindenburgdamm 30, 12 203 Berlin, Germany

9–13 February 1994
European Society of Anaesthesiologists
Brussels, Belgium
Information: Mrs Mary Roe, Options Eurocongress SA, Rue Washington 129, B-1050 Brussels, Belgium

14–18 February 1994
Controversies and Recent Advances in Surgical Pathology
San Diego, California, USA
Information: Armed Forces Institute of Pathology, Education Division, Washington, DC 20 306-6000, USA

17–18 February 1994
New Trends in the Diagnosis and Treatment of Oesophageal Cancer
Amsterdam, The Netherlands
Information: Managing Director, European Postgraduate Gastro-Surgical School, Academic Medical Centre, Meibergdreef 9, 1105-AZ Amsterdam, The Netherlands

21–23 February 1994
Seventh Annual Congress of the North American Society of Phlebology on the Advances in Medical and Surgical Treatment of Venous Disorders
Wilea, Hawaii, USA
Information: North American Society of Phlebology, 523 Encinitas Boulevard, Suite 108, Encinitas, California 92 024, USA

24–26 February 1994
Colorectal Disease in 1994: An International Exchange of Medical and Surgical Concepts
Fort Lauderdale, Florida, USA
Information: The Cleveland Clinic Educational Foundation, Department of Continuing Education, 9500 Euclid Avenue, Cleveland, Ohio 44 195-5241, USA

2–5 March 1994
3rd International Congress: Immune Consequences of Trauma, Shock and Sepsis
Munich, Germany
Information: Dr E. Faist, Ludwig-Maximilians-Universität Munich, Klinikum Großhadern, Chirurgische Klinik, Marchioninistraße 15, D-8000 Munich 70, Germany

28–29 March 1994
Injury Research Group Meeting
Swindon, UK
Information: Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, Oxford Road, Manchester M13 9PT, UK

11–13 April 1994
Third International Symposium on Budd–Chiari Syndrome
London, UK
Information: Professor K. E. F. Hobbs, University Department of Surgery, Royal Free Hospital, Pond Street, London NW3 2QG, UK

16–19 April 1994
SAGES 1994 Scientific Session and Postgraduate Course – Complications of Laparoscopy and Flexible Endoscopy
Nashville, Tennessee, USA
Information: Society of American Gastrointestinal Endoscopic Surgeons, 117 01 Texas Avenue, Suite 101, Los Angeles, California 90 025, USA

20–22 April 1994
Association of Surgeons of Great Britain and Ireland Annual Meeting
Harrogate, UK
Information: Caroline Ross, Association of Surgeons, The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

29–30 April 1994
Current Management of Rectal Cancer
Florence, Italy
Information: R. Gailli, Organizing Secretariat, OIC, Via A. La Marmora 24, 50 121 Firenze, Italy

8–12 May 1994
8th International Congress on Breast Diseases
Rio de Janeiro, Brazil
Information: Congrex do Brasil, Rua do Ouvidor 60/414, 20 040-030 Rio de Janeiro, Brazil

26–28 May 1994
Surgical Infection Society of Europe 7th Annual Meeting
Vienna, Austria
Information: Professor F. Schulz, c/o Wiener Medizinische Akademie für Ärztliche Fortbildung, Alser Straße 4, A-1090 Vienna, Austria

5–8 June 1994
Society for Vascular Surgery–International Society for Cardiovascular Surgery North American Chapter Joint Annual Meeting
Seattle, Washington, USA
Information: North American Chapter, ISCVS, 13 Elm Street, Manchester, Massachusetts 01 944, USA

8–11 June 1994
Tripartite Meeting of the European Society of Surgical Oncology, British Association of Surgical Oncology and Chirurgische Arbeitsgemeinschaft für Onkologie
Heidelberg, Germany
Information: Dr Th. Lehnert, Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, D-69 120 Heidelberg, Germany

2–6 July 1994
XVth Biennial Congress of the International Society of University Colon and Rectal Surgeons
Singapore
Information: ISUCRS XVth Congress Secretariat, c/o Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 0316

7–8 July 1994
Surgical Research Society Meeting
Glasgow, UK
Information: Professor R. E. Mansel, Department of Surgery, University Hospital of Wales College of Medicine, Heath Park, Cardiff CF4 4XN, UK

22–24 September 1994
VIIIth Edmondo Malan International Surgery Days – Difficult Surgical Problems
Parma and Colorno, Italy
Information: Professor G. C. Botta, Istituto di Clinica Chirurgica Generale e dei Trapianti d'Organo, Viale Gramsci 14, 43 100 Parma, Italy

27–30 September 1994
Third International Conference – Ultrasound Angiography
Oxford, UK
Information: Wolfson Conference Centre, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0NN, UK

2–7 October 1994
World Congress of Gastroenterology
Los Angeles, California, USA
Information: World Congress of Gastroenterology Secretariat, 655 15th Street, NW, Suite 300, Washington, DC 20 005, USA

6–7 October 1994
II International Meeting in General Thoracic Surgery
Barcelona, Spain
Information: RCT Asociados, Aulèstia i Pijoan 12, 08 012 Barcelona, Spain

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The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name, address, and telephone and facsimile numbers of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

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The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

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Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

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Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

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The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

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Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

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Edited by D Fry

There have been considerable advances in the care of patients with peritonitis, including major strides in diagnosis, specific surgical care, anaesthetic techniques and supportive measures, including the use of antibiotics.

However, there are still patients who remain unresponsive, typically those with other serious illnesses. The treatment of such challenging cases requires a reexamination of the entire theory and process of treatment of peritonitis. This book furthers such a reassessment and will be of particular benefit to those involved in the front-line care of peritonitis sufferers.

- comprehensive coverage from pathophysiology to methods of treatment;
- a timely review of peritonitis and its management;
- both scientific and practical questions are covered.

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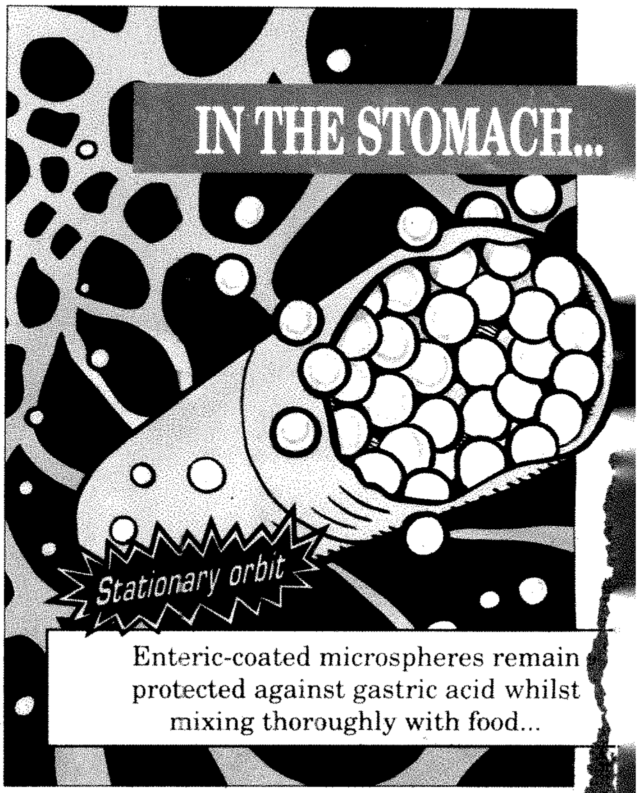
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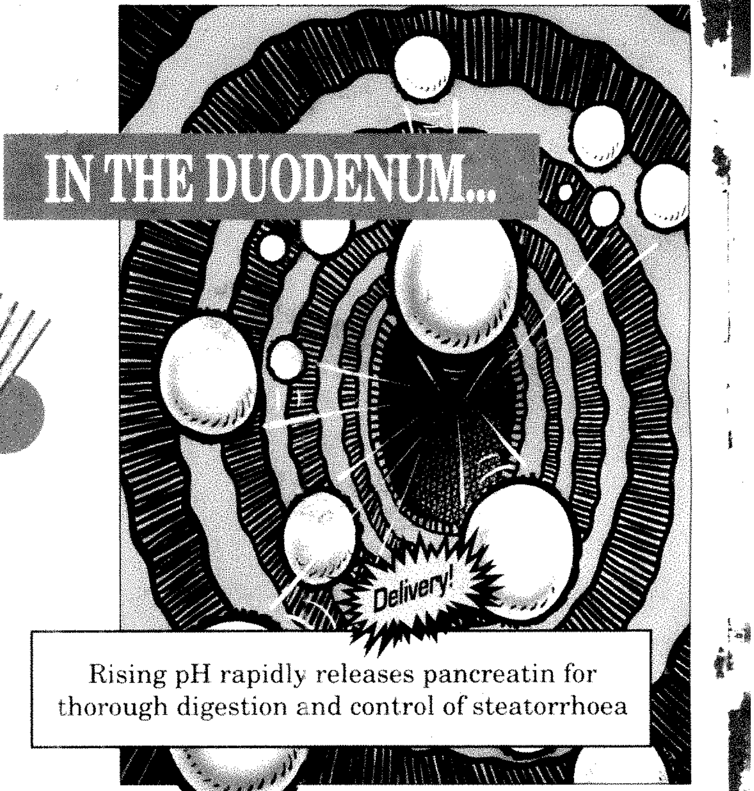
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Peritonitis

Edited by D Fry

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Eurosurgery 93

This abstract book is the second supplement of *The British Journal of Surgery* to contain the abstracts selected for presentation at a Eurosurgery congress. Eurosurgery 93 is the Third European Congress of Surgery, with delegates from over 30 countries of Europe and beyond.

The Secretariat and Standing Committee of Eurochirurgie welcome the collaboration with *The British Journal of Surgery*, which reflects a mutual desire to promote work of the highest quality. Over 1000 abstracts were received from all across Europe and from all disciplines of surgery. Of these, 480 have been selected for publication in this supplement, having been judged for their interest and quality by 130 members of the Scientific Committee of Eurochirurgie.

This supplement will be a permanent record of the high scientific standards of the European Congress of Surgery. I am delighted to see the Congress in London this year, after the successes of Paris and Brussels. I hope to see you again at future meetings, in Berlin in October 1994, and subsequently at Barcelona in 1995 and Rome in 1996.

We look forward to the continued growth and development of Eurochirurgie.

Professor Gérard Champault
Secretary-General of Eurochirurgie/Eurosurgery
Supplement Editor

Acquired immune deficiency syndrome

Reducing the risk of virus transmission during surgery by electronic monitoring of the surgeon–patient barrier

I. Anderson, I. Macintyre, J. Currie and D. Smith, *Western General Hospital, Edinburgh, UK*

The surgeon's gown and gloves are a barrier that prevents virus transmission to or from the patient. A report is made of a new electronic device (Elper) which raises an alarm immediately this barrier is broken.

Fifty operations (laparotomy, 18; intermediate grade procedures (e.g. herniorrhaphy), 16; laparoscopy, 16) were monitored, during which 266 alarms occurred. Bench testing confirmed that 45 alarms (17 per cent) were due to glove holes, 86 (32 per cent) to wet gowns, 115 (43 per cent) to glove porosity and 20 (8 per cent) to other causes. The system detected glove holes with a false-negative rate of only 4 per cent. Holes were more likely to occur during laparotomy than in laparoscopy ($P = 0{\cdot}006$, χ^2 test) or intermediate procedures ($P = 0{\cdot}01$, χ^2 test). Wet gowns were also more common during laparotomy ($P = 0{\cdot}006$, χ^2 test). Alarms due to glove porosity correlated with the duration of operation ($P < 0{\cdot}001$, Kendall's rank correlation).

The surgeon was aware of only 15 per cent of glove holes and response to 54 alarms (20 per cent) was delayed for a median of 16 (range 4–91) min.

The Elper machine reliably detects the frequent episodes of potential viral transmission that occur during surgery. Its use encourages surgeons to take prompt action to restore the barrier that safeguards themselves and their patients.

Human immunodeficiency virus and genital warts as risk factors for anal intraepithelial neoplasia in homosexual men

P.S. Carter, A. DeRuiter*, C. Whatrup, G. Kocjan*, D. Katz*, A. Mindel* and J.M.A. Northover, *Imperial Cancer Research Fund, St Mark's Hospital and *Middlesex Hospital, London, UK*

Studies of the epidemiology of anal cancer have demonstrated a positive correlation with single male status. Recently, a study by Biggar has linked occurrence of anal cancer with homosexual men positive for human immunodeficiency virus (HIV). The present study sought to establish whether a link exists between HIV, genital warts (a recognized risk factor in the development of anal cancer) and the incidence of the potentially premalignant change of anal intraepithelial neoplasia (AIN).

A total of 210 homosexual men were recruited from a single London genitourinary clinic. Each patient completed a questionnaire and was examined for evidence of AIN using an anal smear and an operating microscope. All abnormal areas were biopsied and examined histologically.

Of the 210 patients, 73 (35 per cent) had AIN on histology. HIV status was known in 167 patients; of the 90 positive for HIV, 37 (41 per cent) had AIN, as did 20 (26 per cent) of the 77 negative for HIV. The relative risk of AIN for patients with HIV to those negative for HIV was $1{\cdot}58$ ($P = 0{\cdot}06$). In total, 165 of the 210 patients had anal warts. Of these, 69 (42 per cent) had AIN. This gives a relative risk of AIN for patients with warts to those without of $4{\cdot}70$ ($P = 0{\cdot}00008$).

This study demonstrated a high relative risk of developing AIN for patients with genital warts and a weaker but still increased relative risk of developing AIN for those who are HIV-positive.

Role of biopsy for cerebral lesions in patients with acquired immune deficiency syndrome

M. Iacoangeli, A. Pompucci, R. Roselli, R. Trignani and M. Scerrati, *Institute of Neurosurgery, Catholic University, Rome, Italy*

The involvement of the central nervous system (CNS) in patients with acquired immune deficiency syndrome (AIDS) is a problem of increasing clinical impact. The most common brain complications are toxoplasmosis (50–70 per cent), primary CNS lymphoma (20–30 per cent) and progressive multifocal leucoencephalopathy (PML) (10–20 per cent). Some of these are treatable (toxoplasmosis, neurotuberculosis and bacterial infections); others are diseases in which early diagnosis and therapy can allow prolonged high-quality survival (primary lymphoma). By neuroradiological criteria alone it is not possible to distinguish the broad spectrum of lesions reliably. To assess the potential role and timing of brain biopsy we reviewed our casework.

From October 1991 to December 1992, 12 of 50 (24 per cent) patients with AIDS with focal cerebral lesions underwent brain biopsy (seven stereotactic biopsies and five ultrasound-guided biopsies). In this unit, biopsy is performed early in the course of the disease if the patient does not respond to an appropriate empirical course of antitoxoplasmosis therapy.

All patients had a Karnofsky performance score $>0{\cdot}60$. The diagnosis was confirmed in 11 patients: six PML, three primary lymphoma, one mycotic and one tuberculous abscess. Both techniques were safe (mortality and morbidity rates were zero) and reliable. Early diagnosis and treatment may have a significant impact on the quality and survival of patients with AIDS with cerebral complications.

In conclusion, brain biopsy appears to be indicated for the definitive diagnosis of AIDS-associated CNS lesions.

Complications after major thoracic and abdominal surgery in human immunodeficiency virus-positive patients

S. Martinez, A. Sanchez-Pernaute, L. Diez Valladares, F. Hernando, M. Arguello, J.M. Rodriguez, A.J. Torres and J.L. Balibrea, *Hospital Clinico San Carlos, Madrid, Spain*

Surgeons are required with increasing frequency to perform major thoracic and abdominal operations on patients with human immunodeficiency virus (HIV) and on those with acquired immune deficiency syndrome (AIDS).

Between January 1981 and December 1992, 36 major procedures were performed on 12 asymptomatic HIV-positive patients, 23 patients with AIDS and one patient with AIDS-related complex. There were 32 men and four women. The most frequent risk factor was intravenous drug addiction (35 per cent). Patients were divided into two groups. Group A patients ($n = 14$) were submitted to abdominal operations. Subgroup A1 ($n = 11$) underwent therapeutic procedures for perforated ulcer (three), gastric tumour (two), splenomegaly (four), appendicitis (one) and traumatic rectal perforation (one). Subgroup A2 ($n = 3$) underwent diagnostic procedures for iatrogenic abdominal bleeding (one), obstructive jaundice (one) and retroperitoneal mass (one). Group B ($n = 22$) underwent thoracic surgery. Subgroup B1 ($n = 9$) underwent therapeutic procedures for empyema (five), costal tumour (one), thoracic trauma (one) and cavitated pneumonia (two). Subgroup B2 ($n = 13$) underwent open lung biopsy for diagnostic purposes: a diagnosis was made in eight (62 per cent); five pneumocystis carinii, two Kaposi's sarcoma and one candida. Complications occurred in 23 patients (64 per cent), eight in group A (57 per cent), and 15 in group B (68 per cent). The most common complications in group A were pneumonia in four patients (29 per cent) and sepsis in two (14 per cent). In group B the most frequent complications were bronchopleural fistula in six (27 per cent) and pneumonia in six (27 per cent). The overall mortality rate was 36 per cent (13 of 36): 29 per cent (four of 14) in group A and 41 per cent (nine of 22) in group B. In group B1 the mortality rate was 56 per cent, and 31 per cent in group B2. Mortality rate in patients with AIDS was 83 per cent.

We conclude that open lung biopsy has a high mortality rate in HIV-positive patients, and so this procedure should be reserved for selected patients.

Laparoscopic surgery in patients with acquired immune deficiency syndrome

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The mortality rate for emergency open surgery in patients with acquired immune deficiency syndrome (AIDS) is approximately 70 per cent and that for open cholecystectomy 33 per cent. The morbidity rate is also high as a result of poor wound healing, chest complications and sepsis. In addition,

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open operation carries a significant risk of virus transmission by direct contact. Laparoscopic surgery may reduce these problems. This study reports experience of laparoscopic procedures in 14 patients with AIDS over a 2-year period. There was only one death in the immediate postoperative period. Seven patients underwent laparoscopic cholecystectomy, two for gallstones and five for acalculous cholecystitis. All patients made uneventful recoveries. Five patients presented with an acute abdomen; one patient was found to have a gangrenous appendix which was removed laparoscopically. A further patient had a perforated Kaposi's sarcoma of the small bowel which was resected at open operation. One patient was found to have disseminated intra-abdominal lymphoma with multiple miliary nodules in the liver. Active therapy was withdrawn and the patient died 3 days later. In two patients peritoneal adhesions were found to be the cause of the acute abdominal pain and they underwent laparoscopic adhesiolysis. There were two further operations: a staging laparoscopy with liver biopsy for high-grade lymphoma and a laparoscopic cholecystojejunostomy for AIDS sclerosing cholangiopathy with ampullary stenosis. These data suggest that laparoscopic surgical techniques are associated with greatly reduced mortality and morbidity rates compared with open surgery and are most applicable to the patient with AIDS.

Appendix

Laparoscopic management of appendicitis: analysis of a consecutive series of 100 cases

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Between January 1991 and January 1993, 100 laparoscopic appendicectomies have been performed by two experienced laparoscopic surgeons. The aim of this work was to assess the feasibility, efficacy and possible advantages of this new technique in cases of appendicitis.

Operating time varied from 20 to 90 min. Mean age of patients was 28·4 (range 13–75) years. The series included 11 patients with chronic appendicitis, 41 with acute appendicitis and 22 with perforated appendicitis, with 16 localized and six generalized peritonitis. Conversion to laparotomy because of technical difficulty was necessary in six patients.

There were no postoperative collections or fistulas and two minor and transient parietal infections. No general postoperative complications were observed. Mean postoperative hospital stay was 2·3 days. The advantages of laparoscopic appendicectomy include complete peritoneal lavage in patients with peritonitis, decrease of postoperative parietal defects and infections, easier access to an ectopic appendix, concomitant treatment of any associated pathology, a comfortable postoperative period and anaesthetic advantage in young women.

In conclusion, these results indicate that laparoscopic appendicectomy performed by experienced surgeons is a safe technique in acute appendicitis.

Ultrasonography in suspected acute appendicitis

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Ultrasonography of the right iliac fossa enhances the diagnostic accuracy of acute appendicitis. In a prospective study in 1989 at Danderyd Hospital it was demonstrated that an experienced ultrasonographer soon learns the special technique with graded compression to evaluate the appendix. The aim of this study was to determine whether diagnostic accuracy was the same when ultrasonography was performed by a radiologist who had performed more than 100 examinations compared with radiologists with less experience.

During 1992, in a prospective study, 127 unselected patients underwent ultrasonographic evaluation for the diagnosis of acute appendicitis. Surgery was performed on 59 patients. The histological and ultrasonographic findings were correlated. The expert ultrasonographer had a diagnostic accuracy of 85 per cent (28 of 33 cases) while the less experienced ultrasonographers had an accuracy of 85 per cent (22 of 26). However, it should be mentioned that the expert acted as a teacher to the other radiologists and this probably improved their diagnostic accuracy.

In conclusion, ultrasonographic evaluation certainly has its place in patients with suspected acute appendicitis. The graded compression method is highly reliable. It seems that inexperienced ultrasonographers soon reach a high diagnostic accuracy if taught by an expert in this field of ultrasonography.

Appendicectomy audit in a district general hospital

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A total of 69 consecutive patients underwent operation with a diagnosis of appendicitis in the first 6 months of 1991. Five case notes were not retrieved. The median age of 64 of the patients studied was 29 (range 5–71) years. The male to female ratio was 33:31. The majority of men (76 per cent) were younger than 25 years of age with only 3 per cent being older than 55 years, whereas 58 per cent of women were younger than 25 years and 6 per cent were older than 55 years of age. Of all patients, 55 per cent presented with acute appendicitis within 24 h of onset of symptoms, whereas 17 per cent presented more than a week after the onset of symptoms. The majority of patients (97 per cent) were general practitioner (GP) referrals and most (93 per cent) were operated on within 24 h of admission. Median (range) hospital stay was 4 (2–8) days. A total of 63 per cent were diagnosed as having acute appendicitis by the GP, and 22 per cent were referred by the GP as uncertain, non-specific abdominal pain (NSAP). On admission the diagnosis of acute or complicated appendicitis was made by the surgeon in 86 per cent of cases, offering NSAP for only 3 per cent. Surgical registrars performed the majority of these operations (69 per cent), whereas a minority of 17 per cent and 14 per cent were performed by senior house officers and consultants respectively. In 83 per cent the operative diagnosis agreed with the histology. False negatives were seen in 10 per cent and false positives in only 7 per cent. The histological findings were 69 per cent acute inflammation and 13 per cent normal appendix. Of patients, 91 per cent took antibiotics, with a median of 3 days cover; 18 per cent had only preoperative antibiotic cover, 21 per cent had only postoperative and 61 per cent had both preoperative and postoperative antibiotics. Anticoagulant therapy was given in 6 per cent. The postoperative complication rate was only 2 per cent.

In conclusion, the conventional care provided by district general hospitals offers a high standard of treatment with a very low complication rate, immediate surgical intervention, a high rate of accurate diagnosis and, on average, a short hospital stay.

Practical score to aid in decision making in doubtful cases of appendicitis

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The diagnosis of appendicitis is not always easy and this is evidenced by the high negative laparotomy rate. During recent years different procedures have been utilized to assist in questionable cases; of these methods, few acceptable scoring systems remain.

The aim of the present study was to design a simple scoring system and to use it prospectively in order to evaluate its feasibility and real value as an aid in surgical decision making.

A total of 360 patients who had undergone appendicectomy were analysed to identify historical, clinical and laboratory findings that allowed differentiation between patients with acute appendicitis (81·4 per cent) and patients who had histologically non-inflamed appendices removed (18·4 per cent).

Seven single criteria were found to be significantly different (white blood cell count, percentage neutrophils, sex, location of first pain, diarrhoea, rebound tenderness and contracture). A weighting for each of the predictive factors was calculated using sensitivity, specificity and Bayesian probability. The scoring system was performed with the different weights and a cut-off point established the score that designated patients for observation and those for surgery.

The score was prospectively applied in 166 consecutive patients who had had appendicectomy, 134 (80·7 per cent) with acute appendicitis and 32 (19·3 per cent) without. The scoring system indicated intervention in 113 patients, six of whom had a normal appendix. Therefore, the use of this method could have decreased the negative laparotomy rate to around 5 per cent with a specificity of 0·81 and a sensitivity of 0·80. Scoring systems could become the ideal complementary method in diagnoses of appendicitis, being cheaper, easier and faster to use than any other approach.

Appendicectomy: laparoscopy *versus* McBurney

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One hundred patients, 57 women and 43 men, with a mean age of 26·3 (range 15–71) years were admitted to the emergency room over a period of 9 months with a presentation of straightforward acute appendicitis. Fifty were treated by McBurney's surgical approach and 50 by laparoscopy. The distribution of the two groups was according to the availability of equipment and the experience of the on-call surgeon in laparoscopic surgery. Although non-randomized the two groups had comparable medical background, symptomatology, topographical and pathological distribution of the appendix. There was no mortality.

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Patients operated on by laparoscopy had a significantly shorter return of gut transit (18·3 *versus* 29·4 h); they had less morbidity (1 *versus* 7 per cent, $P = 0.001$) especially for abdominal wall abscesses (0 *versus* 16 per cent, $P = 0.001$). The overall rate of conversion is 12 per cent, but this has progressively diminished with experience (from 22·2 to 6·2 per cent). Operative time was also higher (64·1 *versus* 39·3 min, $P = 0.02$) early in the study, becoming comparable at the end of the study. Finally, laparoscopy has reduced the rate of ablation of macroscopically normal appendices (from 10 to 2 per cent).

The laparoscopic approach to the appendix seems to be the method of choice because of its advantages in the obese, for the ablation of atypical location, for its low morbidity and the economic impact of the reduction of hospital stay and convalescence in non-specific abdominal pain in young women. It avoids 20 to 30 per cent unnecessary appendicectomies. Finally, it constitutes an ideal teaching model for laparoscopic surgery.

Fine-catheter peritoneal cytology for acute abdominal pain

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For many abdominal emergencies, the diagnosis is unclear. In such cases fine-catheter peritoneal cytology (FCPC) is reported to be a useful diagnostic aid[1].

All abdominal emergencies have been allocated to a control or study group for 5 months, according to the admitting surgical consultant. The control group was managed conventionally, those under study were subdivided: group 1 comprised patients requiring operation on clinical grounds; group 2 included those considered not to require operation; and group 3 consisted of patients for whom the decision for operation was uncertain. Group 3 patients underwent FCPC unless dictated otherwise by conventional exclusion criteria. Men with a positive FCPC underwent mini-laparotomy, women diagnostic laparoscopy followed by laparotomy if indicated.

There were 151 controls and 171 under study. Fourteen of 15 patients in group 3 underwent FCPC; two were unsuccessful, there was one false-positive and one false-negative result, and one patient refused. FCPC reliably predicted the management in ten other patients. The patient with the false-positive result underwent unnecessary operation, as did a further five from group 1. Operation was delayed in the false-negative patient. There were seven unnecessary operations among controls.

FCPC has a useful but limited role in managing the acute abdomen.

1. Vipond MN, Paterson-Brown S, Tyrrell MR, Coleman D, Thompson JN, Dudley HAF. Evaluation of fine catheter peritoneal cytology of the peritoneum as an adjunct to decision making in the acute abdomen. *Br J Surg* 1990; **77**: 86–7.

Carcinoid tumours of the appendix

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The records of 181 patients with carcinoid tumour of the appendix seen during the 10-year period 1977–1987 were analysed retrospectively to determine the indications for right colectomy and the significance of intermediate histopathological forms of tumour. Appendicectomy was the only treatment in 146 cases. Right hemicolectomy was performed in 35 patients: initially in seven with one death after operation, and secondarily in 28 without mortality or morbidity. Colectomy was initially indicated in seven cases for bulky tumours of the base of the appendix invading the caecum or for associated carcinoma of the right colon. The 28 secondary colectomies were for tumours that were statistically larger and more invasive than those treated by simple appendicectomy and/or for intermediate forms (five cases). There were five cases of residual tumour in secondary hemicolectomy specimens. In 11 of the 181 carcinoid tumours (6 per cent), the intermediate type of tumour was associated with mucin production (seven adenocarcinoids and four carcinoids with mucocele). Of the seven patients with adenocarcinoid, there was one death at 2 years and one patient is alive with metastases.

Other than a size > 2 cm and basal localization, this study suggests that the presence of mucin-producing cells is a further indication for secondary right hemicolectomy.

Biliary

Haemobilia: a rare cause of acute cholecystitis

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Haemobilia is generally thought to be caused by trauma to the liver. Ruptured hepatic artery aneurysm, liver tumours, suppurative cholangitis, pyogenic and amoebic abscesses, and anticoagulation are also reported to result in haemobilia. A patient with haemobilia that caused acute cholecystitis is reported.

An 18-year-old man had right upper quadrant pain 8 days after mitral valve replacement (MVR). He had received anticoagulation after the operation. Ultrasonography and computed tomography revealed a distended gallbladder with a wall thickness of 10 mm, which contained inspissated bile showing a double contour. The common bile duct was found to be dilated. The patient was treated conservatively but the symptoms kept recurring and he was operated on 40 days after MVR. At operation, there was a reddish-brown haematoma combined with inspissated bile in the gallbladder and the common bile duct. Histopathological examination confirmed the diagnosis of haemobilia and acute cholecystitis. T tube cholangiography revealed cystic dilatations of the hepatic ducts at the confluence which were thought to be choledochal cysts of type IV. The patient had an intra-abdominal haemorrhage and haemobilia on the second day after surgery due to anticoagulation. He was treated conservatively, after which the T tube was removed and he was discharged. He is now being followed for the cystic dilatations of the bile ducts.

Although haemobilia resulting in acute cholecystitis but not jaundice and haemobilia associated with cystic dilatations of the bile ducts are extremely rare conditions, they should be considered in patients on anticoagulation therapy who have symptoms of acute cholecystitis.

Non-filling of the gallbladder during intravenous cholangiography is associated with conversion of laparoscopic to open cholecystectomy

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Between August 1990 and February 1993, 96 patients considered suitable for laparoscopic cholecystectomy underwent preoperative intravenous cholangiography (IVC) to exclude asymptomatic stones in the common bile duct (CBD). As well as outlining the CBD, IVC demonstrated opacification of the gallbladder in 64 patients; in the remaining 32 patients, contrast did not enter the gallbladder.

Laparoscopic removal of the gallbladder was successfully accomplished in 84 patients. The remaining 12 (12 per cent) required conversion of the laparoscopic procedure to open cholecystectomy. Of the 64 patients whose gallbladder filled during preoperative IVC, only four (6 per cent) required a laparotomy. However, eight of the 32 patients in whom the gallbladder did not fill during cholangiography required conversion to open cholecystectomy ($\chi^2 = 5\cdot25$; $P = 0\cdot02$).

Non-filling of the gallbladder during preoperative IVC is associated with a fourfold increase in the incidence of abandoning laparoscopic and conversion to open cholecystectomy.

Effects of experimental external biliary drainage and extrahepatic cholestasis on bacterial translocation

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The effects of bile duct ligation and cessation of bile flow into the gut, by bile duct cannulation, on bacterial translocation were determined. Three groups each containing eight rats were studied: sham ligated, bile duct ligated and bile duct cannulated, in which external biliary drainage was performed, using a 0·45 × 25 mm catheter. The aim of the latter procedure was to determine whether cessation of bile flow into the gut, under conditions of normal liver cellular function, contributed to bacterial translocation. Rats were killed after 7 days. Serum glutamic–oxaloacetic transaminase, serum glutamic–pyruvic transaminase and alkaline phosphatase levels were determined. Liver, spleen, mesentery, ileum and caecum were studied microbiologically and histologically. Levels of liver enzymes were significantly raised ($P < 0\cdot05$) in rats with a ligated bile duct, compared with other groups. Bacterial translocation was 87·5 per cent whereas no translocation was detected in other groups. Histologically, the intestinal mucosal barrier was compromised with accompanying pericholangiitis and ductal proliferation in the liver. There was caecal bacterial overgrowth. By contrast, in rats with external biliary drainage the intestinal mucosal barrier and liver were completely normal and there was no bacterial overgrowth in the caecum. Thus cessation of bile flow into the gut, when the liver was not under stasis, did not promote bacterial translocation.

Treatment of postoperative bile duct stricture using vascularized jejunal patches

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In six patients with a history of recurrent cholangitis, a stricture of the extrahepatic bile duct was diagnosed by endoscopic retrograde cholangiography (ERC) as the source of infection. The strictured duct was 3–5 cm long. Cholecystectomy in four patients and bilioenteric anastomoses in the other two caused the recurrent bile duct infections leading to the strictures. Because of the length of the strictures, a vascularized jejunal patch was used for reconstruction of the bile duct after splitting of the stricture. In the follow-up 5–15 years after operation, whereas four patients did not report any problems regarding their disease, two patients had recurrent infections twice a year. In all patients, the bile duct was visible at endoscopy. None of the patients had raised bilirubin levels, the bile flow was not disturbed and no fibrosis of the bile duct was seen.

Experience in these six patients suggests that reconstruction of strictured bile ducts after splitting using a jejunal patch is an effective method of treatment for strictures >2 cm long. The advantages of bilioenteric anastomosis are the possibility of visualizing the bile duct by ERC and of obtaining bile fluid for microbiological analysis in the case of cholangitis.

Selective cholangiography before laparoscopic cholecystectomy

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Common bile duct (CBD) stones occur in 8–20 per cent of patients with cholelithiasis. Preoperative detection allows endoscopic duct clearance before laparoscopic cholecystectomy. Criteria established in a previous study[1] were used to identify patients for selective cholangiography before laparoscopic cholecystectomy in 100 cases. Patients were categorized into three groups according to the risk of choledocholithiasis: group I (low risk): CBD < 7 mm, normal liver function tests (LFTs); group II (moderate risk): CBD ≥ 7 mm or mild derangement of LFTs; group III (high risk): clinical jaundice (bilirubin > $50\,\text{mmol l}^{-1}$) or stone seen in the CBD on ultrasonography.

Clinical and biochemical assessment was performed 12 months after surgery. Fifty-three patients (group I) had no further CBD imaging; 38 (group II) underwent intravenous cholangiography with 11 proceeding to endoscopic retrograde cholangiopancreatography (ERCP) and nine (group III) had primary ERCP. CBD stones were found in 11 cases. One patient required postoperative ERCP but no retained CBD stones were demonstrated in any patient.

The results from this study support the use of selective CBD imaging before laparoscopic cholecystectomy.

1. Tulloh BR, Eyers PS, Adams DCR, Poskitt KR. Preoperative ultrasonography and liver function tests to identify patients for selective cholangiography. *Br J Surg* 1992; **79**: S7 (Abstract).

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Critical assessment of 'biliary' symptoms

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Many patients suffer persisting symptoms after cholecystectomy. A recent study showed that 43 per cent complained of pain or dyspepsia at > 1 year after operation. Several authors have failed to identify which symptoms are specific to gallbladder stones. A questionnaire survey was carried out on 164 patients referred for ultrasonography (US) for investigation of 'biliary' symptoms and 218 patients 1–2 years after open cholecystectomy for gallstones (184 of 218 patients (84 per cent) responded).

Multivariate analysis confirmed that stones were more likely if the pain was severe or followed by jaundice. Absence of stones was suggested by age < 60 years, reflux, sharp pain or pain not relieved by vomiting. A simple model allows rapid calculation of a score that predicts 90 per cent of patients without stones, with a certainty of 90 per cent.

Careful symptom assessment could reduce unnecessary requests for US. After cholecystectomy the most common symptoms were flatulence (48 per cent), pain (30 per cent), fullness (34 per cent) and bloating (28 per cent). Heartburn (21 per cent) and reflux (14 per cent) were also reported. Manning's criteria for irritable bowel syndrome (IBS) were satisfied in 47 per cent of patients with pain after cholecystectomy.

This study confirmed the high incidence of symptoms after cholecystectomy. IBS occurs in one-third of patients thought to have gallstones, and is more often after cholecystectomy. Careful analysis of symptoms may identify patients likely to benefit from cholecystectomy.

Management of choledochal cysts in adults

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This study reports five cases of type I choledochal cysts (two men and three women, aged 20–84 years), operated on in this department during the period 1978–1991. Symptoms were recurrent upper abdominal pain in all patients, jaundice in two and ascending cholangitis in four. A palpable mass was present in one patient and gallstones were seen in two. Diagnosis was established by intravenous cholangiogram or ultrasonography, in one case during operation. The surgical procedure was Roux-en-Y choledochocystojejunostomy in three cases, cyst excision with Roux-en-Y hepaticojejunostomy in one, and choledochocystoduodenostomy in an elderly patient. Concurrent cholecystectomy was performed in two cases.

After operation, no major complications occurred apart from one case of respiratory failure in an elderly patient, treated successfully in the intensive care unit. During the follow-up period (2–15 years), one patient had recurrent episodes of ascending cholangitis within 2 years of cystoduodenostomy. Late results are very good in the other four patients (4–15 years after the operation). Cystojejunostomy or cyst excision with hepaticojejunostomy are the most frequently reported surgical procedures in the literature. The therapeutic actions in this study were in agreement with published recommendations for therapy.

Indications for and value of choledochoduodenostomy

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The long-term effectiveness of choledochoduodenostomy was investigated in a retrospective analysis of 166 patients. From January 1971 to December 1989, 224 patients underwent side-to-side choledochoduodenostomy. Fourteen (6·2 per cent) died in the immediate postoperative period and another nine (4·0 per cent) from malignancy not previously detected. Thirty-five patients were lost to follow-up and the remaining 166 were followed for 3–14 years.

Choledocholithiasis, ampullary stenosis, echinococcosis, intrahepatic stones and postoperative stricture were the indications for choledochoduodenostomy. The diameter of the common bile duct (CBD) ranged from 18 to 43 mm. The overall morbidity rate was 24 per cent. The long-term follow-up revealed 15 (9 per cent) patients with symptoms 6 months to 11 years after choledochoduodenostomy. Two had mild attacks of pancreatitis and 13 had episodes of cholangitis. In four patients cholangitis resolved spontaneously and in three endoscopic retrograde cholangiopancreatography showed impacted stones which were treated by endoscopic sphincterotomy. At operation in six patients, two fibrous anastomotic strictures were demonstrated and the other four patients were believed to have a sump syndrome. Two transduodenal sphincteroplasties and four Roux-en-Y conversions were performed. One patient died and the others are symptom-free. These results show that choledochoduodenostomy is an effective long-term treatment for non-neoplastic obstructing lesions of the distal CBD.

Value of repeated reconstruction for recurrent benign biliary stricture

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Since 1965, 101 operations for benign iatrogenic biliary duct stricture have been performed, including 61 Roux-en-Y hepaticojejunostomies. All operated patients are under permanent clinical observation, with a mean follow-up of 12·5 years. Restricture of previous anastomosis was an indication for reoperation in nine patients. In all patients, including those who underwent successful reoperation, the cumulative late patency rate evaluated clinically, biochemically and by HIDA scan was 90 per cent. In seven of nine reoperated patients, no abnormalities were found, with a follow-up period of up to 19 years. One patient has had four reoperations; the last operation was a Hepp's procedure and right duct anastomosis with stent into the jejunum.

Early reconstructive surgery for recurrent biliary stricture after hepaticojejunostomy is recommended to cure patients with iatrogenic benign lesions. Continued postoperative follow-up is required.

Intraoperative choledochoscopy: the most effective method for biliary tract exploration

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A consecutive series of 453 common bile duct (CBD) explorations was studied to examine the efficacy of various methods of imaging the biliary tract. Patients were divided into two groups: group A comprised 335 patients before the advent of choledochoscopy and group B consisted of 118 patients treated after the introduction of intraoperative choledochoscopy in 1990.

Choledochoscopy was performed for the following clinical indications: current or previous obstructive jaundice, cholangitis, pancreatitis, stenosing papillitis, biochemical evidence of obstructive jaundice, ultrasonographic evidence of CBD dilatation or choledocholithiasis and endoscopic retrograde cholangiopancreatographic identification of multiple bile duct stones. Intraoperative indications included multiple and small gallstones and a dilated cystic duct, dilated CBD, and palpable stones.

The authors have performed 87 choledochoscopies using an Olympus choledochoscope. Nine patients had unsuspected bile duct stones that would have been missed without choledochoscopy.

Before the introduction of choledochoscopy, 11 patients in group A underwent reoperation for retained stones (3·3 per cent), while in group B there was no incidence of missed stones.

Postoperative trans T tube choledochoscopy was successfully performed in three patients. Complications were not seen. Flexible choledochoscopy is a safe and simple method of exploring the biliary tract. It significantly reduces the incidence of missed stones.

Role of bupivacaine in decreasing postoperative pain and pulmonary complications

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The effectiveness of bupivacaine was investigated for control of postoperative pain in 90 selected patients, who underwent elective cholecystectomy. Patients were randomized into three groups of 30 patients. In group 1, 50 ml 0·5 per cent bupivacaine was injected into the incision layers before closure. In group 2, a thin epidural catheter was inserted between the peritoneum and muscle layers. During the first postoperative 60 h 150 ml 0·5 per cent bupivacaine was given through an infusion pump. In group 3, 50 ml 0·9 per cent NaCl was injected into the incision before closure. The three groups were compared using postoperative visual analogue pain score, postoperative need for analgesia, respiratory function and duration of hospital stay. Bupivacaine was more effective than 0·9 per cent NaCl in reducing the need for postoperative pethidine in the first 24 h after surgery. The median (range) pethidine required was 60 (20–75) mg in group 1, 55 (25–60) mg in group 2 and 100 (25–150) mg in group 3. In the later postoperative period there was no significant difference. The amount of analgesia required was the same for injection or infusion of bupivacaine in the first 24 h ($P > 0{\cdot}05$). There were no significant differences between the three groups regarding respiratory function or duration of hospital stay. Bupivacaine administered into the wound reduced early postoperative pain but had no effect on postoperative recovery.

Obstructive jaundice: Wallstent metallic endoprosthesis

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Permanent prostheses in the bile duct provide good palliation for malignant biliary non-operable obstructive jaundice. Between April 1990 and August 1991, 25 Wallstent biliary prostheses were implanted in 20 patients with biliary obstruction. This new prosthesis has a large internal diameter and can be inserted percutaneously. Indications, morbidity and mortality were studied. The mean age of the 20 patients (11 men) was 68·2 (range 33–84) years. Nineteen had malignant lesions: ten cholangiocarcinoma, five pancreatic cancer and four metastatic nodes near the ampulla of Vater. One obstruction was benign in a patient with two stenoses of an enterobiliary bypass. Early complications (< 72 h) (biliary sepsis, pancreatitis and subcapsular haematoma) occurred in 30 per cent of the cases. Late complications were cholangitis without obstruction of the prosthesis (20 per cent) and prothesis obstruction (30 per cent). Eleven patients (55 per cent) died, two from cholangitis, one from intestinal bleeding, four from progression of carcinoma and four from other causes.

Predicting the need for cholangiography during laparoscopic cholecystectomy: selective *versus* routine

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The aim of this study was to assess the feasibility of a policy of selective cholangiography using a simple method for predicting the need for cholangiography during laparoscopic cholecystectomy.

The study comprised three different analyses: retrospective analysis (discriminant analysis) of factors associated with common bile duct (CBD) stones in a subpopulation of patients ($n = 204$) submitted for elective open cholecystectomy (control group 1); prospective evaluation of the same factors in patients ($n = 177$) submitted for elective open cholecystectomy (control group 2); and prospective evaluation of these factors in a consecutive group of patients submitted for elective laparoscopic cholecystectomy.

Results are expressed in terms of the diagnostic properties of the prediction obtained from the discriminant analysis of each subgroup of patients.

	Control group 1	Control group 2	Laparoscopic cholecystectomy group
Sensitivity	74·7	76·9	40·0
Specificity	69·9	82·6	94·1
Accuracy	71·9	81·4	92·6
Undetected stones	10·7	5·1	1·7
Unnecessary peroperative cholangiography	17·3	13·6	5·7

Values are percentages

In conclusion, the present study demonstrates the feasibility of a policy of selective cholangiography for patients submitted for open and laparoscopic cholecystectomy using an equation that accurately predicts which patients are at risk of harbouring CBD stones. Using this system the need for peroperative cholangiography can be routinely assessed for each patient. Only asymptomatic CBD stones are not detected by the system (1–7 per cent of unsuspected stones in patients submitted for laparoscopic cholecystectomy) although this figure compares favourably with false-negative and false-positive rates obtained in patients undergoing routine peroperative cholangiography.

Biliary peritonitis after T tube removal: experimental study of pathogenic factors (latex *versus* silicone with systemic corticosteroid administration)

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The aims of the present study were to compare the degree of postoperative peritoneal adhesion (PPA) conditioned by two different materials (latex and silicone) and to analyse the influence of corticosteroids on PPA.

Forty Wistar rats were divided into four groups: group I ($n = 10$) were a latex control group; group II ($n = 10$) had latex and corticosteroids; group III ($n = 10$) were a silicone control group; and group IV ($n = 10$) had silicone and corticosteroids. A 2-cm midline mini-laparotomy to position a 2-cm segment of T tube in the subhepatic space was performed. In groups I and II the tube was latex, and in groups III and IV silicone. Corticosteroids were administered to the rats in groups II and IV, 30 mg kg^{-1} day^{-1} of intramuscular methylprednisolone for 30 days. The rats were killed after 30 days, and the PPAs were measured using a point scale which considered: (1) mobilization of the tube; (2) percentage of surface covered outside the tube; (3) percentage of lumen occupied inside the tube; (4) degree of tenacity; and (5) existence of vascularization. The maximum score possible for each rat was 10 points and minimum 0. The non-parametric Kruskal–Wallis and Mann–Whitney tests were used to analyse the results. The overall scores of the rats in each group were: group I (latex), 82 points; group II (latex, corticosteroids), 46 points; group III (silicone), 33 points; and group IV (silicone, corticosteroids), 18 points. Silicone caused fewer PPAs than latex ($P < 0{\cdot}001$). Corticoid administration significantly reduced the PPA rate in both the latex ($P < 0{\cdot}001$) and silicone groups. Silicone conditions PPAs to a lesser extent than latex and corticosteroids reduce the PPA rate with both latex and silicone.

Agenesis of the gallbladder in adult patients: a diagnostic problem

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Agenesis of the gallbladder without extrahepatic biliary atresia is a rare congenital disorder. The incidental finding during surgery of two cases of gallbladder agenesis over the past 15 years at this institution prompted a review of the diagnostic problem. Both patients were symptomatic, ultrasonography showed false-positive gallstones and the gallbladder was not visualized using cholangiography. The first patient underwent an open laparotomy and the second a laparoscopic operation. In spite of modern diagnostic methods such as ultrasonography and cholangiography, gallbladder agenesis cannot be diagnosed before surgery. Diagnosis is possible by intraoperative cholangiography or at autopsy. The incidence of this anomaly in the authors' experience is reported.

Place of routine cholangiography at laparoscopic cholecystectomy: a prospective study

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The development of laparoscopic cholecystectomy has reduced the proportion of patients undergoing routine operative cholangiography because of the technical problems. The necessity of obtaining a cholangiogram should not be influenced by the procedure of cholecystectomy. The aim of this study was to assess the feasibility and performance of laparoscopic cholangiography (LC) during the treatment of symptomatic gallstones.

Between January and December 1992, 100 patients with symptomatic gallstones eligible for laparoscopic cholecystectomy were studied prospectively. Of these, acute cholecystitis was present in 26 patients. There were two conversions to open cholecystectomy. LC was attempted in 87 of the 100 cases, but was not attempted in 13 because of iodine allergy or a previous endoscopic sphincterotomy. Cholangiography was successful in 72 patients (83 per cent). The 15 failures were because of a narrow cystic duct in ten and cystic duct valves in five. According to preoperative clinical, biological, ultrasonographic and cholangiographic findings, 68 of 72 cholangiograms were normal. In the four abnormal peroperative cholangiograms there was abnormal biliary anatomy (no cystic duct) in one case, a common bile duct stone in one case and cystic duct stones in two. In the two former cases conversion to open cholecystectomy was performed. In the two latter cases, laparoscopic cholecystectomy was performed after removal of the cystic duct stones.

In conclusion, LC permits detection of: (1) abnormalities of biliary anatomy, usually unsuspected on routine preoperative investigations, avoiding severe bile duct injuries; (2) cystic duct stones, whose laparoscopic treatment is generally easy; and (3) common bile duct stones, usually suspected before operation.

LC can be carried out simply and effectively in most cases, but failures are unpredictable. Other methods of preoperative bile duct evaluation (endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography) have to be evaluated.

Caroli's disease: therapeutic procedures and late results

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Caroli's disease is a rare condition characterized by multiple segmental cystic dilatations of the intrahepatic bile ducts. The existence of the ectasia is usually recognized through the resulting complications, such as cholelithiasis, abscess of the liver, septicaemia, cirrhosis and portal hypertension. The risk of malignant degeneration is approximately 10 per cent. For this reason, radical resection is considered the ideal therapy, although it is possible only when a single liver lobe is affected. Experience in the treatment of 16 patients with Caroli's syndrome is reported. The group consisted of nine men and seven women (mean age 42 years). Twelve patients had cholangiolithiasis, and in five secondary biliary cirrhosis had developed, which in three cases resulted in portal hypertension with liver failure. Eight of the patients had previously undergone cholecystectomy elsewhere. A 17-year-old patient also underwent a portocaval shunt. Surgical revisions were performed on seven patients. In six cases, a choledocholithotomy was carried out with extrahepatic and intrahepatic stone extraction. This was combined with cholecystectomy in three patients and with papillotomy in two. Partial hepatectomy was possible only in two cases. Ten patients had endoscopic procedures, nine had papillotomy, eight underwent extrahepatic and intrahepatic stone extraction and internal drains were inserted in six. In a follow-up period of 12 years less than 25 per cent of the patients were asymptomatic. Among these were both patients who underwent partial hepatectomy. In all other patients, recurrent cholangitis, sometimes with cholangiolithiasis, was the main complaint. This led to a requirement for repeated palliative and endoscopic drainage procedures. The mortality rate at 12-year follow-up was 26 per cent, which indicates the poor prognosis in this condition.

Cholecystectomy by microlaparotomy and minilaparotomy

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A total of 412 consecutive microlaparotomy and minilaparotomy cholecystectomies were performed between 13 December 1990 and 31 January 1993. These minimally invasive cholecystectomy procedures were developed as alternatives to laparoscopic and conventional cholecystectomy. Microlaparotomy surgical removal of the gallbladder was done through a 2–3-cm vertical midline incision between the xiphoid and umbilicus. This technique was used for 296 operations (71·8 per cent). Minilaparotomy cholecystectomy with a 3–4-cm vertical incision was performed in 93 patients (22·3 per cent) and with a 4–6-cm vertical midline incision in 23 (5·6 per cent) patients of whom 17 had choledocholithiasis, four had accessory bile ducts and three had abscess formation around the gallbladder. There was one death (0·3 per cent), three early reoperations (0·7 per cent) and four late reoperations (1·0 per cent). Of the 296 patients with a 2–3-cm incision, 294 were discharged between 1 and 3 days after surgery. Except for those requiring early reoperation and some very elderly patients, all patients were discharged by the fifth day. All patients with diseased gallbladders are potential candidates for these procedures.

Management of obstructive cholecystitis with minilaparotomy

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A total of 412 modern minilaparotomy cholecystectomies were performed between 13 December 1990 and 31 January 1993; 99 patients (24 per cent) had acute or chronic obstructive cholecystitis. These cases were divided into three groups. Group 1 comprised 27 patients who presented within 10 days of the acute attack. There were four cases of acute Mirizzi syndrome with jaundice and seven of necrosis of the gallbladder wall. There was no morbidity. These patients were discharged 2 or 3 days after surgery. In group 2, 34 patients presented between 10 days and 6 weeks of the acute attack. In nine cases, there was abscess formation around the gallbladder; in one of these, there was bile leakage and subhepatic bile collection from Luschka's duct. This patient required reoperation 2 days after surgery. Two cases of wound suppuration and four of common bile duct stones were encountered. The 38 patients in group 3 presented with a history longer than 6 weeks, with one or more episodes of acute attack. There was one death. In one instance, Schloffer's tumour compressed the hepatic and common bile ducts. Three instances of spontaneous biliary–enteric fistula, six of common bile duct stones and three of wound suppuration were encountered.

Bile culture of 366 patients undergoing biliary surgery

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This study of bile samples from 366 patients taken during biliary surgery performed in the Southern General Hospital, Glasgow, during the 5-year period from January 1985 to December 1989 was carried out to establish the incidence of positive bile cultures and the prevalence and frequency of cultured organisms therefrom. The relationship between positive culture, age of patients and magnitude of the surgery was also explored.

The results showed 17 different organisms in a variety of combinations. Culture was positive in 19·9 per cent of cases, of which 69·9 per cent grew one type of organism, 23·3 per cent grew two types and 6·8 per cent grew more than two. Organisms were grown in the following order of frequency: *Escherichia coli* (45·2 per cent), streptococci (16·4 per cent), *Clostridium*, mainly *C. perfringens* (15·1 per cent), *Klebsiella* (9·6 per cent) and *Bacteroides* (8·2 per cent). The number of positive cultures increased in relationship to the magnitude of the surgical procedure undertaken. Cultures were positive in 17·5 per cent of patients undergoing simple cholecystectomy, in 23·6 per cent undergoing cholecystectomy and cholangiography, and in 44·4 per cent undergoing cholecystectomy with exploration of the common bile duct. The incidence of positive cultures increased with increasing age with a steep rise in those >60 years which was maintained to a level of 75 per cent in patients aged >80 years.

Management of cholangitis: retrospective study of 160 cases

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Between 1 January 1970 and 20 January 1992, 160 patients (107 women and 53 men, mean age 67 (range 28–94) years) were treated for cholangitis. Of these, 147 had a simple form (SC) and 13 an acute suppurative form (ASC). Six patients (4 per cent) did not undergo surgery (medical treatment in two cases, endoscopic sphincterotomy (ES) in four). The remaining 154 patients were operated on, 26 of them (17 per cent) after preoperative ES. Common bile duct (CBD) exploration was carried out through a choledochotomy in 147 cases (95 per cent) and via the cystic duct in three cases; in four cases, peroperative cholangiography confirmed CBD evacuation after ES. External biliary drainage (EBD) was performed in 127 cases (82 per cent) and biliary–enteric anastomosis (BEA) in 22 (14 per cent); in five cases (3 per cent), only the cystic duct was ligated. EBD and BEA rates (respectively 75 and 25 per cent before 1980) became 87 and 8 per cent from 1980 (P not significant). The overall mortality rate was 12·5 per cent, being 22 per cent in 1970–1979, 8 per cent in 1980–1989 and 0 per cent since 1990 ($P < 0\cdot05$). The mortality rate was 7 per cent (ten of 147) in SC and 77 per cent (ten of 13) in ASC ($P < 0\cdot01$). ASC mortality rate decreased from 100 per cent (seven of seven) in the first decade to 50 per cent (three of six) in the second. Mortality rate was higher after BEA (23 per cent (five of 22)) than after EBD (12 per cent (15 of 127)) ($P < 0\cdot05$). It was 7 per cent (two of 30) when preoperative ES was performed against 14 per cent (18 of 130) without it ($P < 0\cdot05$). The morbidity rate was 27 per cent (43 cases), being 34 per cent (20 of 58) in the first decade, 21 per cent (18 of 84) in the second and 28 per cent (five of 18) in the last 2 years ($P < 0\cdot05$). It was 31 per cent after EBD and 14 per cent after BEA ($P < 0\cdot01$). Cholangitis is a serious complication of CBD stones. The prognosis has improved over the past decade and preoperative ES appears to improve the outcome.

Surgical management of injuries to the extrahepatic biliary system

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Fifty-four patients operated on between 1950 and 1990 were divided into three groups according to the injury, time to diagnosis and time to corrective procedure. The first group consisted of 18 patients in whom reconstruction of the bile ducts was performed during the primary operation. The second group comprised nine patients in whom injury was diagnosed in the early postoperative period. The third group of 27 patients had restenoses after reconstruction performed in other hospitals. The primary operation, localization of the injury, diagnostic procedures and operative treatment of the bile duct injuries were analysed in each group. Thirty-two patients reviewed at least 2 years after corrective surgery were studied as a long-term follow-up group. According to clinical examination, laboratory tests, radiography and biliary scintigraphy, long-term results were satisfactory in 24 patients. The authors believe hepaticojejunostomy Roux-en-Y to be the procedure of choice in the majority of cases.

Targeted delivery of antibiotic in biliary surgery

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A new method has been developed experimentally and applied clinically that targets delivery of antibiotic to the liver and biliary system by means of autologous erythrocyte ghosts. Intravenous infusion of erythrocyte ghosts containing a single dose of antibiotic is performed twice a day.

The clinical trial consisted of three treatment groups. Group 1 comprised 190 patients with acute cholecystitis and with a high risk of needing urgent operation. Group 2 comprised 17 patients with intrahepatic biliary abscesses. Group 3 comprised 33 patients with acute cholangitis. The effect of the new method was also studied on the immune status of patients and the pharmacokinetics of antibiotics in the bile.

The results have shown greater effectiveness of a targeted delivery method in comparison with conventional methods of antibiotic infusion. The new method creates a high and prolonged antibiotic concentration in the bile, and reduces the recovery time of patients with acute cholecystitis. All patients with intrahepatic abscesses and with acute cholangitis were treated successfully without operation.

Breast

Ultrasonographic localization of impalpable breast tumours after screening

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Accurate localization of a tumour is imperative before excision biopsy for impalpable breast lesions seen on screening mammography. Ultrasonographic localization has the advantages of being simple, quick and non-invasive.

In a 3-year period from September 1989, 26 953 women have been screened for breast carcinoma. Of these, 185 have required localization before biopsy; 159 (86 per cent) were performed using a wire localization technique and 26 (14 per cent) were performed using ultrasonography alone. These latter 26 women were of mean age 57 (range 50–64) years. The location of these tumours were: 13 upper inner quadrant, nine upper outer quadrant, one lower outer quadrant, two lower inner quadrant and one lower mid-breast. Twenty-two of the 26 were malignant; the four benign lesions were two sclerosing lesions and two fibroadenomas. The mean (95 per cent confidence interval) maximum diameter of tumour diagnosed by ultrasonography compared with the histological specimen was 10·6 (8·5–12·7) *versus* 11·1 (8·9–13·3) mm with a correlation (r_s) of 0·87. In the malignant cases the mean maximum diameter of tissue excised was 63·0 (95 per cent confidence interval 57·2–65·9) mm. Complete excision was obtained in 21 of the 22 patients with malignant disease by a single operation. One patient with two foci identified on ultrasonography required subsequent mastectomy.

Ultrasonography alone has been used successfully as a means of preoperative localization in selected cases before excision biopsy of a breast tumour.

Non-palpable breast lesions: correlation between radiology findings and histological features

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Non-palpable breast lesions are very non-specific and require biopsy, usually with mammographic needle localization, to provide histopathological confirmation of their nature.

Over a period of 19 months 52 biopsies of non-palpable breast lesions were performed, with 22 carcinomas (42 per cent) and 30 benign tumours (58 per cent). Correlations between mammographic lesions and histopathological features were: (1) 26 (50 per cent) had microcalcifications (seven carcinomas and 19 benign lesions); (2) six (12 per cent) had mammographic nodules (three carcinomas and three benign lesions); (3) 12 (23 per cent) images showed nodules with microcalcification (eight carcinomas and four benign lesions); (4) three (6 per cent) images demonstrated architectural abnormality (one carcinoma and two benign lesions); (5) two (4 per cent) images showed architectural abnormality with microcalcifications (one carcinoma and one benign lesion); and (6) three (6 per cent) normal mammographies revealed carcinoma (subsequently diagnosed by cytology).

This study showed a higher malignancy rate in non-palpable breast lesions compared with the reported literature. The highest incidence of malignancy was in non-palpable mammographic nodules.

Perioperative blood transfusion and prognosis after operation for breast cancer

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The Danish Breast Cancer Cooperative Group collects data on all patients operated on for breast cancer. These prospective data were used with retrospectively collected transfusion data to test the hypothesis that perioperative blood transfusion increases the rates of recurrence and death after mastectomy. In the period 1977–1982, 1599 patients in Copenhagen underwent mastectomy. Of 228 patients who received perioperative transfusion, the disease recurred in 110 (48 per cent), compared with 647 (47 per cent) of 1371 patients not having transfusion ($P = 0·85$). The 5-year recurrence-free survival rate was 54 per cent in the transfused group *versus* 60 per cent in the non-transfused group ($P = 0·44$). For overall and cancer-specific survival the rates were 67 *versus* 73 per cent ($P = 0·24$) and 69 *versus* 76 per cent ($P = 0·12$). The patients having transfusion had a higher prevalence of risk factors. When the effects of these risk factors were accounted for using Cox multiple regression analysis, the effect of blood transfusion on recurrence and death was eliminated. This study does not support the hypothesis that perioperative blood transfusion increases the risk of recurrence and death after mastectomy for breast cancer.

Diagnostic reliability of a combined approach of physical examination, mammography and fine-needle aspiration biopsy in patients with breast cancer

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Breast cancer is a common malignancy in women. Physical examination is the first step and the most widely used diagnostic method. Mammography, an important adjunct for proving the diagnosis of breast cancer, has a low accuracy rate in detecting small masses. Recently fine-needle aspiration biopsy (FNAB) has gained acceptance as an adjuvant diagnostic procedure to physical examination and mammography for the evaluation of breast masses. Various accuracy rates have been reported for these three methods.

In this study the accuracy of a combination of physical examination, mammography and FNAB in diagnosing breast tumours in a consecutive, unselected series of women referred to the department for breast lesions was assessed. During the study period, 184 women with breast cancer were examined. Physical examination performed by the specialist surgeons was graded as malignant, suspected malignant and benign. Mammography results were classified as in the physical examination. The results of FNAB were reported as unsatisfactory, benign, non-diagnostic, malignant and suspicious. The results obtained were compared with the histopathological examination results of the specimens.

Using physical examination 92·9 per cent of the lesions were evaluated as malignant or suspicious. The false-negative diagnosis rate was 7·1 per cent. Mammography showed 94·9 per cent of the lesions as malignant or suspicious and its false-negative rate was 5·1 per cent. By FNAB, 94·8 per cent of the breast lesions were diagnosed as malignant or suspicious and the false-negative rate was 5·2 per cent. The accuracy rate of the combination of three diagnostic methods was 100 per cent. As a result, when these three methods were used in combination, diagnosis of the breast cancer was made accurately.

Psychological treatments for anxiety in breast cancer: initial findings

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Initial results are presented that form part of an ongoing longitudinal study measuring the degree of anxiety experienced by women after breast cancer has first been diagnosed. A number of psychological interventions aimed at reducing this anxiety have been initiated. Patients are randomized on a weekly basis to one of three treatment groups: relaxation, taught by volunteers; befriending, by psychotherapists; and a control group from which the current level of care can be assessed. Each patient is asked to complete a series of questionnaires before surgery and at regular intervals afterwards.

Initial findings suggest that there are no significant differences between groups with respect to anxiety. The Mental Adjustment to Cancer scale appears to be more sensitive and reveals some modest group differences. However, the small number of patients per group precludes making any

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firm conclusions. For approximately one-third of patients, waiting for breast cancer surgery and the pathological results of that surgery can be very stressful. However, such levels of anxiety gradually diminish with time.

Investigation and treatment of breast cancer in England and Wales

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The treatment of breast cancer is controversial. To ascertain how surgeons in England and Wales treat this disease a questionnaire was sent to all consultant general surgeons listed in the Medical Directory in 1992. A total of 985 questionnaires were sent and 592 replies were received, a response rate of 60 per cent. Regarding the treatment of a premenopausal woman with a 2-cm carcinoma in the upper outer quadrant, 78 per cent indicated that they would treat this conservatively, 17 per cent would offer the patient the choice of conservation or mastectomy and only 5 per cent indicated that they would advise mastectomy. Regarding the treatment of the axilla, a full axillary dissection was recommended by 41 per cent and axillary sampling by 36 per cent. Surgeons were more than twice as likely to leave the axilla untreated in postmenopausal (8 per cent) than in premenopausal (3 per cent) patients. A total of 37 per cent of surgeons would treat an elderly patient with breast cancer by lumpectomy and tamoxifen compared with 34 per cent who would use tamoxifen alone. Mastectomy would be recommended by 69 per cent for a patient who developed local recurrence after conservative treatment for breast cancer. Finally, 91 per cent of surgeons believe that outpatient follow-up is worthwhile, but 70 per cent would not perform any regular staging investigations apart from mammography if the patient remained asymptomatic. This study provides an important insight into the current treatment of this common disease.

Breast-conserving therapy in 832 patients

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Between 1977 and 1990, 832 breast-conserving treatments in 814 patients with breast cancer (median age 49·4 years) have been carried out according to a prospective controlled trial in the region of Basel. Although the surgical procedures were done by a number of surgeons, the radiotherapeutic treatment and histopathological review were limited to one centre and one pathologist respectively.

Of the patients 46·4 per cent had stage pT_1pN_0 disease, 18·2 per cent pT_1pN_1, 16·0 per cent pT_2pN_0 and 13·9 per cent pT_2pN_1 respectively (5·5 per cent carcinoma *in situ*).

At a median follow-up of 3·4 years, according to the Kaplan–Meier method the estimated 5-year survival rate was 91 per cent for all patients and reached 88 per cent for those with invasive ductal cancer, 96 per cent for those with invasive lobular cancer, and 95 per cent for those with medullary cancer. The overall local recurrence-free survival rate is 94 per cent at 5 years. The corresponding figures are 97 per cent for node-negative, 89 per cent for node-positive, 96 per cent for pT_1 and 91 per cent for pT_2 patients. Of the patients 84·5 per cent are distant disease-free at 5 years (91 per cent pN_0, 70 per cent pN_1).

In this analysis, tumour-free margins of the specimen were found to be statistically significant in local recurrence-free survival (P = 0·00008). Overall, in 43 of 832 patients a local failure occurred after breast-conserving treatment. After salvage therapy, the 5-year survival rate reached 63 per cent for this group of patients.

Smooth *versus* textured breast implants: a rodent study

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The withdrawal of polyurethane foam-covered breast prostheses has intensified the search for an alternative implant with a low capsular contracture (CC) rate. Preliminary clinical studies comparing CC around smooth and textured implants suggest that surface texturing reduces the incidence of contracture. Animal studies are contradictory.

This study was designed to investigate the contractility of capsules formed around smooth and textured surface silicone gel prostheses in an animal model of CC. The prostheses (15 mm × 5 mm) were implanted subcutaneously in female Hooded Lister rats (mean(s.d.) 250(25) g) and the capsules harvested after 7 or 28 days. The capsules were analysed histologically (Masson's trichrome stain) and functionally (contractility response to a myofibroblast stimulant).

The capsules around textured surface prostheses were more adherent, thinner (P < 0·05), and structurally less organized than those around smooth prostheses. Their reactivities (mg tension) to 4 mg mepyramine are shown in the table.

Day	Smooth (n = 8)	Textured (n = 8)	Mann–Whitney *U* test	
			P	U
7	7·9 (3·1–9·7)	1·8 (0·9–1·9)	0·01	10
28	2·0 (1·5–2·1)	1·1 (0·0–1·6)	0·03	14

Values are mean (range)

Textured surface implants induced significantly less reactive capsules. These results support the preferential use of textured surface prostheses.

Immunomodulatory potential of *Mycobacteria phlei* in primary breast cancer

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Mycobacteria are known to have immunomodulatory effects. A purified cell wall extract of *Mycobacteria phlei* (MCWE) may circumvent the problems associated with live whole-cell preparations. A pilot study investigated the potential of MCWE to modulate the *in vitro* immune response of patients with primary breast cancer. A dose–response curve was first established to determine the optimum dose of MCWE to be used. Peripheral lymphocytes and monocytes were separated over Ficoll from ten volunteers. The lymphocyte blastogenic response to phytohaemagglutin (PHA) and concanavalin A (Con A) was measured by counting the cells after pulsing them with tritiated thymidine. MCWE was added to the cells in 96-well microtitre plates in concentrations ranging from 0·1 to 200 µg ml^{-1}. Maximum blastogenesis was observed at 5 µg ml^{-1}. The blastogenic response was reduced significantly (P < 0·0001) at doses above 50 µg ml^{-1}, suggesting toxicity at high doses. Similar responses were not seen with lipopolysaccharide (LPS). The same experiment was repeated in six patients with primary breast cancer and two controls. MCWE and LPS were used at a concentration of 5 µg ml^{-1}. Two patients were significantly immunosuppressed to the mitogens PHA and Con A (P<0·05) when compared to the controls. These two patients had a significantly better blastogenic response than the four immunocompetent patients (P < 0·05) in response to MCWE. This suggests that a purified cell wall extract of *Mycobacteria phlei* has potential as an immunotherapeutic agent and may have an adjunctive role to play in the management of immunosuppressed patients with breast cancer.

Conservative surgery in breast carcinoma: experience over 13 years

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Conservative surgery represents an important step forward in the treatment of breast carcinoma, providing the same level of disease control as traditional surgical therapies but reducing the deformity and mutilation to which patients are subjected. This consequently increases their acceptance of the disease and its treatment. Application implies, in our experience, observing three principles: (1) tumour excision with an acceptable safety margin; (2) complete axillary dissection, preferably by a separate incision; and (3) adjunctive radiotherapy of the remaining breast.

From 1979 to 1992, 183 patients in our service received conservative surgery for breast carcinoma. Eligibility criteria were T_1 N_0 M_0 clinically staged tumours, excluding those located centrally. Analysed were age distribution, laterality, quadrant distribution in the breast, risk factor assessment (family history of breast cancer, premenopausal/postmenopausal status, length of fertile period up to the appearance of the tumour, parity), histological classification of the tumours, lymph node metastases and hormonal receptor status. Finally presented are actuarial survival rates at 10 years for the global series: 82·4 per cent overall, 71·3 per cent without evidence of disease and 90·5 per cent without local recurrence. Actuarial survival according to lymph node status is also presented.

Patient satisfaction with breast reconstruction after cancer surgery

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Breast reconstruction after cancer surgery has evolved from reconstruction of the entire breast after mastectomy to the more recent techniques of restoration of shape and symmetry after conservative breast surgery. These procedures with variation in the extent, duration and timing of surgery influence patient satisfaction. A total of 54 patients underwent reconstructive surgery with prosthetic replacement (18 patients), reduction mammoplasty (25) or myocutaneous flap reconstruction (11). The main reason for requesting reconstruction was to improve body image. Satisfaction was assessed on a scale from 1 (very satisfied) to 5 (very dissatisfied) in relation to the shape, size and scarring after reconstruction. Overall outcome of the procedures was compared in the three groups. The mean period of stay in hospital was 2·7 days for the reduction group, 3·8 days for the replacement group and 9·8 days for the flap reconstruction group. The mean overall satisfaction score was 1·6 in the reduction group, 2·0 in the flap reconstruction group, and 2·2 in the replacement group. The incidence of complications was highest in the replacement group (15 per cent) with infection and extrusion of the prostheses being the main problems. It is concluded that reconstruction by reduction mammoplasty after conservative surgery provides a more satisfactory outcome than replacement mammoplasty.

Breast-conserving therapy for ductal carcinoma *in situ*

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As the use of breast cancer screening programmes has grown there has been a marked increase in the detection of ductal and lobular carcinoma *in situ*. This study asked what influence tumour excision, axillary dissection and consecutive irradiation as treatment for ductal carcinoma *in situ* (DCIS) has on the incidence and localization of non-invasive and invasive recurrence. From 1977 to 1990, 893 breast-conserving procedures were performed for breast cancer. In 55 patients (6·2 per cent) the histological diagnosis was carcinoma *in situ* (50 DCIS). The median follow-up is 3·5 (range 0·4–13·4) years. In the group of 50 DCIS five local recurrences (10 per cent; three non-invasive, two invasive) occurred. Two patients developed carcinoma in the contralateral breast. There were two deaths (disease-free at autopsy) in this group. Breast conservative therapy is a treatment option for DCIS. The local recurrence rate is not low, therefore careful follow-up by clinical examination and mammography is mandatory.

Cardiovascular

En bloc transplantation of the heart and entire thoracic aorta

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Rat cardiac and aortic transplantation have been useful tools to study rejection and tolerance. However, thus far, these techniques have been used separately as allograft models. The purpose of this study was to develop an *en bloc* 'heart–entire thoracic aorta' (H–TAO) transplant model to study immunological phenomena in both organs, in the same animal. This model was developed and based on 15 transplants in DA and Lewis (DA × Lew) rats.

The H–TAO was harvested after thoracotomy as follows: (1) division of the TAO at the diaphragm and clamping of the thoracic inferior vena cava; (2) ligature and division of the superior vena cava; (3) dissection and division of the left branch of the pulmonary artery; (4) perfusion of the heart–lungs with 4°C Ringer's solution (2–3 ml); (5) excision of the lungs; and (6) separation of the entire TAO by ligature and division of its branches. After the TAO had been flushed, the H–TAO unit was transplanted to the recipient's abdominal vessels in a conventional microsurgical manner. Before the abdominal vascular clamps were released, a vascular clamp was placed on the TAO, allowing for controlled perfusion of the heart without blood loss, by permitting ligature of hitherto unseen lumbar arteries.

Donor and recipient operations lasted for a maximum of 15 and 30 min respectively. There was no technique-related mortality. While the hearts of unmodified recipients were rejected at 6 days, the TAO did not reveal grossly the rejection features seen in the cardiac counterpart. Strikingly, the lumen of these TAOs remained free from thrombus and debris. Also noted was a shortening of the initial aortic length at the time of cardiac rejection.

Immunosuppressed recipients are under observation for the development of chronic rejection. This model will help further to define immune-mediated events occurring in the two organs in one recipient.

Ejection fraction *versus* clinical index for predicting cardiac problems after infrarenal aortic reconstruction

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Following infrarenal aortic reconstruction, the cardiac morbidity and mortality rates are high. A prospective comparison of a clinical risk index and ejection fraction measurement for predicting postoperative cardiac events has been carried out.

Forty-eight consecutive patients were assessed by the Detsky modification of the Goldman risk index. Ejection fractions were also measured using both echocardiography and ^{99m}technetium. There were 31 patients with abdominal aortic aneurysms and 17 with occlusive disease. Within 30 days, three patients (6 per cent) experienced four major cardiac events (three left ventricular failures and one fatal myocardial infarction). In addition, 14 patients (29 per cent) experienced 15 minor cardiac events (11 arrhythmia and four ST segment depression). As the cardiac risk index rose, so did the likelihood of cardiac events ($P < 0{\cdot}01$, multiple regression analysis). Ejection fraction, determined by either method, failed to correlate with subsequent cardiac events.

In conclusion, the clinical cardiac risk index predicts postoperative cardiac events in patients undergoing aortic reconstruction whereas calculation of the ejection fraction is unhelpful.

Metabolic and haemodynamic determination of left ventricular function in isolated pig hearts during sustained cold chemical cardioplegia and storage

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Left ventricular function was evaluated during sustained cold chemical cardioplegia and hypothermic storage.

Forty-eight Danish Landrace pigs, weighing 70–80 kg, were used. Seven groups of pig hearts were evaluated. Group 1 hearts excised from slaughterhouse pigs were subjected to 9 min of warm ischaemia before induction of 171 min cold chemical cardioplegia. Group 2–7 hearts were excised from pigs under general anaesthesia. After induction of intracellular-type cold chemical cardioplegia, using a single infusion, the hearts were stored hypothermically at 4°C for 30 ($n = 8$), 90 ($n = 8$), 180 ($n = 8$), 270 ($n = 7$), 360 ($n = 6$) and 1080 ($n = 3$) min in groups 2–7 respectively. Bretschneider no. 3 cardioplegic solution was used. The hearts were thereafter mounted in a modified Langendorff model and reperfused for 120 min. The reperfusion medium was a 1:1 mixture of blood and Ringer's chloride. Functional parameters measured were: contractility (+dP/dt), relaxation (−dP/dt), developed left ventricular pressure, left ventricular systolic pressure, left ventricular end-diastolic pressure, coronary blood flow, heart rate and heart work. Metabolic parameters measured were: adenosine 5'-triphosphate (ATP) and glycogen content, lactate extraction and myocardial oxygen uptake. The frequency of DC-conversion and of pacing were also determined.

The functional and metabolic recovery during the reperfusion period were the same for hearts in groups 2–5. However, the functional recovery and myocardial oxygen uptake in hearts from groups 1, 6 and 7 were significantly lower than in hearts from groups 2–5. The myocardial release of lactate from hearts in groups 1 and 7 was significantly higher during reperfusion than that from hearts in groups 2–5. The most sensitive functional parameters were +dP/dt and −dP/dt. Tissue glycogen was significantly lower in groups 4–7 than in group 2 hearts (a 70 per cent decrease in glycogen was observed after 18 h, $P < 0{\cdot}01$). Tissue glycogen declined linearly with time of ischaemia. The ATP content of group 7 hearts was significantly lower than in group 2 hearts.

In conclusion, cold chemical cardioplegia and hypothermic storage with Bretschneider's solution containing procaine is safe for periods of up to 4·5 h.

Interatrial pressure reversal measured in patients after coronary artery bypass surgery

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Reports on patency of the open foramen ovale resulting from an increased pulmonary resistance are common. These shunts can lead to a decrease in partial pressure of oxygen, which cannot be corrected with a higher fraction of inspired oxygen. Other clinical studies stress that patients with an open foramen ovale are at risk of paradoxical emboli and decompression sickness. As it is currently believed that the foramen is functionally closed during the cardiac cycle, and that the lung can filter venous emboli, no satisfactory explanation can be found in the literature to justify the paradoxical nature of emboli through a patent foramen.

To analyse the haemodynamic basis for interatrial shunts, right and left atrial pressures were measured simultaneously after coronary artery bypass grafting in 17 patients with sinus rhythm and normal left ventricular function, using catheters placed during operation. Recordings were made both during spontaneous breathing and positive-pressure ventilation.

A cyclical pressure reversal, in which right atrial pressure exceeded left atrial pressure, was reproducibly recorded. It started a mean(s.e.m.) 215(5) ms after the onset of the electrocardiographic P wave, lasted 179(14) ms and had a maximal amplitude of 4·1(0·3) mmHg. During the expiration phase of spontaneous breathing and the inspiration phase of positive-pressure ventilation, the onset of the pressure reversal occurred later; its duration was shorter and its amplitude smaller.

These observations demonstrate the presence of a cyclical interatrial pressure reversal and show that the breathing mode affects the time course and amplitude of this reversal.

Transfusion after coronary artery bypass surgery

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Risks associated with homologous blood transfusion are well documented. The incidence of homologous blood transfusion and the effects on

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haematological parameters in a cardiothoracic unit where three different transfusion policies exist were investigated. In group A, patients were transfused at a haemoglobin level of $7\,g\,dl^{-1}$ or less, group B at $8\,g\,dl^{-1}$, and group C at $9\,g\,dl^{-1}$. A prospective study was made of 120 patients. Intraoperative and postoperative blood loss, preoperative haematocrit, immediate and 4-day postoperative haematocrit, and the need for fresh autologous and homologous blood transfusion were recorded. Intraoperative and postoperative blood losses were similar in all three groups. Group A had a significantly decreased incidence (6·2 per cent) of homologous blood transfusion compared with the other groups ($P < 0·01$) and group B (40 per cent) had significantly fewer transfusions than group C (75 per cent; $P < 0·01$). Despite this there was no difference in the preoperative or postoperative haematocrits between the three groups. Patients who received autologous blood transfusion but who did not require homologous blood transfusion had significantly less postoperative blood loss ($P < 0·05$) and significantly higher postoperative haematocrits ($P < 0·01$). The overall amount of blood transfused (1·08 units) was less than previously reported. However, the results suggest that the institution of a predetermined blood transfusion policy and the use of autologous blood could further reduce the incidence of homologous blood transfusion without affecting haematological parameters.

Aprotinin and thrombolytic therapy in cardiac surgery

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Despite better testing of donors, allogenic transfusions still imply risks for patients. A case of intraoperative thrombosis of an aortocoronary saphenous vein graft on the left anterior descending artery, occurring in a patient treated with an aprotinin protocol (2×10^6 KI units in the priming volume and 5×10^5 KI units every hour of cardiopulmonary bypass) is detailed. Thrombectomy of the left anterior descending artery using a 2-Fr Fogarty catheter and revision of the anastomosis with a new segment of vein was performed. Then 1 mg recombinant tissue plasminogen activator diluted in 10 ml was injected selectively into the graft. Balloon-pump counterpulsation was used to wean off the extracorporeal circulation. The patient had an uneventful recovery and there were neither electrocardiographic signs nor cardiac enzyme modifications indicative of myocardial infarction.

It is strongly believed that this episode of thrombosis of the coronary artery was related to the use of aprotinin. The authors now use low-dose aprotinin (2×10^6 KI units in the priming volume) in patients with a high risk of perioperative bleeding.

A 10-year review of the stability of Carpentier's mitral valvuloplasty in 150 patients with mitral insufficiency

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Mitral valve reconstruction resulting in conservation is now considered to preserve left ventricular function better than mitral valve replacement. Reconstruction techniques are complex and difficult to acquire. Over a 10-year period from 1 January 1983 to 31 December 1992, 150 mitral valve reconstructions were performed by one self-taught surgeon. All patients had dominant mitral regurgitation. There were 69 men and 81 women of mean age 62 (range 24–72) years. The aetiology of valve disease was rheumatic (72 patients), degenerative (69), endocarditis (four), ischaemic (three) and hypereosinophilia (two). Operation was performed using cardiopulmonary bypass with moderate hypothermia (28°C) and crystalloid cardioplegia throughout. Annuloplasty was performed in 148 patients using a Carpentier ring (142 patients), DeVega (three), Duran (two) and St Jude Medical (one). Fifty-two patients had some form of leaflet resection; there were 50 posterior leaflet resections. Associated procedures were performed in 47 patients: vein graft (23 patients), aortic valve replacement (12), atrial septal defect repair (five) and tricuspid valve repair (five).

The 30-day hospital mortality rate was 2·0 per cent (three patients). Isolated mitral Carpentier annuloplasty (102 patients) carried a mortality rate of 1·0 per cent (one patient). Two patients (1·3 per cent) required immediate valve replacement at first operation. Actuarial 1- and 5-year survival rates were 98·0 and 96·8 per cent respectively. Six late valve replacements (4·2 per cent) were performed, four within the first 2 years. The valve reoperation-free rate was 92 per cent at 5 years and 89 per cent at 8 years. Progression of rheumatic valve disease was the main cause (90 per cent) of late failure. Mitral reconstruction combined with prosthetic ring annuloplasty gives a stable and durable repair with a very low operative mortality and reoperation rate for valve failure. Failure is more likely to occur where there is rheumatic valve disease and is unrelated to the initial learning phase.

Colon and rectum

Diverticular disease in patients under 50 years of age

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Seventy-seven patients under 50 years of age were admitted with acute diverticular problems. The total number of admissions was similar for each year. The mean(s.d.) age at admission was 41·7(6·3) years and there was no significant sex difference. Some 25 per cent of patients had previously been admitted with diverticular disease.

At presentation, 79 per cent had abdominal pain, 22 per cent a change in bowel habit, 21 per cent rectal bleeding, and 30 per cent were on a high-fibre diet, but only 3 per cent had taken non-steroidal anti-inflammatory drugs. The mean(s.d.) white cell count was $11{\cdot}3(5{\cdot}4) \times 10^{9}\,\mathrm{l}^{-1}$ for the whole group, but was significantly higher in 18 patients who required surgery ($13{\cdot}7(7{\cdot}8) \times 10^{9}\,\mathrm{l}^{-1}$) than in the rest ($10{\cdot}6(4{\cdot}3) \times 10^{9}\,\mathrm{l}^{-1}$), $P < 0{\cdot}05$. Radiological assessment was by plain radiography (66 per cent), contrast enema (79 per cent), ultrasonography (29 per cent) and computed tomography (1 per cent). Colonoscopy was performed on 21 per cent of individuals. By a combination of clinical and radiological review, diagnosis was made in 98 per cent of patients.

Surgical intervention for control of the disease process was required in 23 per cent of patients; 61 per cent of these had had one or more previous admissions for an acute diverticular episode. The indications were: overwhelming peritonitis (67 per cent), bowel obstruction (11 per cent) and troublesome fistulas (17 per cent). Early postoperative mortality (30 days) was zero. The majority of patients (78 per cent) had resection of the diseased colon as Hartmann's procedure (44 per cent) or resection and primary anastomosis (34 per cent). Only 16 per cent were treated by peritoneal irrigation and drainage of the septic focus.

Diverticular disease in young people runs an aggressive course, and early surgery is advised.

Intraoperative colonic irrigation in the treatment of left-sided large bowel obstruction

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The surgical treatment of acute left colonic obstruction continues to be controversial. Since the introduction of intraoperative colonic irrigation, resection and primary anastomosis has become an acceptable method in the treatment of obstructing lesions of the left colon. This paper reports the use of such intraoperative antegrade colonic irrigation in the management of left-sided large bowel conditions requiring emergency surgery.

During the 2-year period from 1990 to 1992, 30 consecutive patients (17 women and 13 men) with a mean age of 72·8 (range 45–89) years underwent emergency operation for obstructing lesions of the left colon. All patients were managed by intraoperative colonic irrigation. A Foley catheter was inserted into the caecum through either a caecostomy or the appendix stump; the colon was rapidly washed out with 3–5 litres of warm saline until the effluvium was clear. In all cases, a colonic resection and primary anastomosis without colostomy was performed. The site of the large bowel obstruction was sigmoid in 14, descending colon in four and rectum in two patients, and the cause of the obstruction was large bowel carcinoma in 23, diverticulitis in five and volvulus in two. There were two postoperative deaths (7 per cent): one myocardial infarction and one inhalation pneumonia. No postoperative fistula was observed. Mean hospital stay was 195 (range 9–35) days.

The results of this study suggest that intraoperative colonic irrigation is an effective method, enabling the surgeon to perform a primary anastomosis with reasonable safety after emergency resection of selected distal colonic lesions.

First impressions with the biofragmentable anastomosis ring: report of 15 cases

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Fifteen patients underwent large bowel resection with anastomosis using the biofragmentable anastomosis ring (BAR) between May and December 1992; eight men and seven women, with a median (range) age of 64 (22–83) years. Fourteen patients had neoplasms and one colonic angiodysplasia. Tumour location was sigmoid in seven, right colon in four, splenic flexure in one, descending colon in one and rectosigmoid in one. Preoperative antegrade intestinal lavage was carried out in 14 patients and intraoperative lavage in one patient with intestinal obstruction. Seven sigmoidectomies, four right hemicolectomies, two left hemicolectomies, one subtotal colectomy and one anterior resection were performed. Anastomosis was made with BAR size 28 in nine cases, size 31 in five cases and size 25 in one case. Postoperative ileus lasted a median of 3·7 days with expulsion of the BAR occurring a median (range) of 22 (15–28) days after operation. There were three anastomotic leaks with one death caused by the leakage.

Use of the BAR is easy and time sparing, but does not avoid complications.

Total abdominal colectomy, mucosal proctectomy and J pouch–anal anastomosis

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Total abdominal colectomy, mucosal proctectomy and ileal J pouch–anal anastomosis is the most suitable and radical treatment of diseases that are precancerous and affect only the mucosa, such as familial adenomatous polyposis (FAP) and ulcerative colitis. Of seven patients (four male, three female, mean age 33 years), four were operated on for FAP and three for ulcerative colitis using this technique. In five patients diverting ileostomy was performed and closed between 35 and 56 (mean 46) days. Postoperative complications were one wound infection, one retrograde ejaculation and one intestinal obstruction. (Intestinal obstruction occurred in one of the two patients without ileostomy.) There was no mortality. All patients except one with retrograde ejaculation are currently well, with no disturbance of urinary or sexual function. The follow-up period was between 6 and 36 (mean 15) months. Continence of faeces was complete in all during the day and night. Average frequency of evacuation was 5–7 times in 24 h. All patients tolerated a full diet and only two used medication to reduce stool frequency.

Role of retinal and endoscopic examination, and DNA analysis in screening for familial adenomatous polyposis

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Increasing awareness of the genetic abnormalities and extracolonic manifestations associated with familial adenomatous polyposis (FAP) has resulted in a multidisciplinary approach to screening for the disease.

Sigmoidoscopy, retinal examination to detect congenital hypertrophy of the retinal pigment epithelium and DNA analysis have been used to adjust the risks for those people in the region born with a prior risk of 0·5. Using Bayes' theorem, risks have been increased in two individuals from 0·5 to 0·998 and reduced in a further 19 individuals to values ranging from 0·0025 to 0·000023. The use of sigmoidoscopy and DNA analysis alone achieved a significant alteration in all but one individual. In this patient, findings on retinal examination reduced the risk from 0·018 to 0·004.

Retinal examination in combination with sigmoidoscopy does not reduce risks sufficiently to alter current screening practice. However, given a favourable DNA result, linkage analysis combined with endoscopy is sufficient to alter risks to such levels that screening practice may be altered.

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Retinal examination is advisable in families in which risks cannot be reduced sufficiently by DNA and endoscopic findings alone, but need not necessarily be performed routinely in all families carrying the FAP gene.

Closing a colostomy with the biofragmentable anastomosis ring

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Twelve patients have been studied; all had a diverting lateral colostomy. There were five cancers of the rectum, one sigmoid injury, one ischaemic colon and five cases of sigmoid diverticulosis. Colostomy closure was performed 8 weeks after the original procedure. There was no technical problem using the recommended technique, which included good dissection and resection of the distal end on each side and application of 2/0 Maxon sutures to fix the colon on the ring on each side. Operating time was 1 h; the postoperative course was uneventful. All patients were able to leave hospital in 4 days.

Anastomotic stenosis after colorectal surgery

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Stenosis arising after colorectal anastomosis is a late complication. The anatomy is uncertain, its frequency is underestimated and its pathogenesis is poorly understood. Reported is experience of the risk factors and endoscopic conservative treatments. A total of 178 colorectal anastomoses were performed from 1989 to 1992: the EEA autostapling device was used in 158 patients (48 using the Knight–Griffen technique, 36 of whom underwent emergency procedures); at follow-up two patients had a small leak, five patients a subclinical pelvic infection. Colonoscopy was performed every 6 months. In all, 71 patients were excluded (49 for pelvic recurrence and were 22 were lost to follow-up). A total of 19 anastomotic stenoses were analysed: 17 were stapled (six with the Knight–Griffen technique) and two were hand-sewn; 18 were located in the extraperitoneal side between 1 and 12 cm. Complications were as follows: anastomotic leakage in two, pelvic infection in two, irradiation in one, obesity in seven, urgent operation in four. Endoscopic treatment was accomplished (five settings on average) using a Hegar thrusting sigmoidoscope, a Foley catheter, balloon dilators, a Savary probe and a papillotomy knife. The results were satisfactory in 14 cases, adequate in three and transient or inadequate in two.

Some risk factors can be minimized by careful technique and new methods of anastomosis; dilatation, using endoscopic treatment, is the safest and easiest technique, and gives the least blood loss.

Effect of parenteral and enteral nutrition on the healing of colonic anastomoses in rats

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The effect of parenteral and enteral nutrition enriched with pectin on the healing of colonic anastomoses in rats was studied. The rate of healing was assessed by bursting pressure and hydroxyproline measurements on the fourth and tenth days after operation following a colonic transection and primary anastomosis. Rats of group 1 were given only water after operation, group 2 received parenteral dextrose and saline solution, group 3 was fed with total parenteral nutrition and group 4 with regular enteral diet. Group 5 received regular enteral diet plus pectin at a low perfusion rate, group 6 received the same diet at a higher perfusion rate (0·2 and $0{\cdot}8\,\mathrm{ml\,min^{-1}}$ respectively). On the fourth day after operation groups 4, 5 and 6 differed significantly from groups 1, 2 and 3 ($P < 0{\cdot}001$). On the tenth day after operation group 6 differed significantly from groups 1–5 ($P < 0{\cdot}001$).

The present data suggest that enteral solutions enriched with pectin perfused at a rate of $0{\cdot}8\,\mathrm{ml\,min^{-1}}$ serve to increase the absorptive surface area for enteral nutrition agents, leading to a higher rate of colonic anastomotic healing.

Emergency intestinal anastomosis in peritonitis

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To evaluate the results of primary intestinal resection and anastomosis performed in patients presenting with peritonitis, 15 patients with a mean age of 59 (range 37–69) years have been studied retrospectively. All patients had emergency operations. Ten patients had localized peritonitis and five had generalized peritonitis that was purulent in three, faecal in one and barium peritonitis in the other. Five sigmoid resections, three ileocaecal resections, three ileal resections, two right hemicolectomies, one left hemicolectomy and one transverse colonic resection were performed. The mean total time of operation was 4 (range 2–7) h. There were no postoperative anastomotic complications. One patient with generalized faecal peritonitis caused by a ruptured caecum died on the first postoperative day from septicaemia.

Three of four patients who had major postoperative complications had generalized peritonitis. The overall mortality rate was 7 per cent and the morbidity rate 27 per cent.

We believe that primary resection and anastomosis in patients with peritonitis is a safe technique.

Hand-sewn *versus* stapled colonic anastomosis

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Conflicting results have been published concerning the advantages of hand-sewn over stapled anastomosis. This study aimed to compare mechanical, biochemical and histological parameters of healing in hand-sewn *versus* stapled anastomosis.

In 24 mongrel dogs a segment of colon was resected and randomized to undergo one-layer hand-sewn or stapled anastomosis. The largest stapler that the bowel could accommodate was used. Six animals, three from each group, were killed at 1, 4, 7 and 28 days after operation. The anastomoses were evaluated for radiological index, bursting pressure, hydroxyproline content and histological appearance. The radiological index was calculated as the ratio of the diameter of the anastomosis to that of the adjacent bowel. Data were compared using the Mann–Whitney *U* test.

	Time after operation (days)			
	1	4	7	28
Radiological index				
Hand-sewn	0·72(0·07)	0·68(0·07)	0·55(0·04)*	0·83(0·08)
Stapled	0·79(0·06)	0·69(0·04)	0·69(0·01)*	0·85(0·08)
Bursting pressure (mmHg)				
Hand-sewn	115(36)	182(12)	243(29)	383(9)
Stapled	153(40)	150(30)	192(9)	360(6)
Hydroxyproline content (µg per mg dry weight)				
Hand-sewn	7·9(1·9)	13·3(1·8)	10·5(0·3)	9·4(2·5)
Stapled	9·3(1·9)	15·2(0·8)	10·7(1·5)	14·2(1·9)

Values are mean(s.e.m.). * $P = 0{\cdot}05$

Mean(s.e.m.) hydroxyproline content in the resected colon of the hand-sewn group was $10{\cdot}3(0{\cdot}9)\,\mu\mathrm{g\,mg^{-1}}$ and $12{\cdot}3(1{\cdot}0)\,\mu\mathrm{g\,mg^{-1}}$ for those undergoing stapling. Histological examination showed no differences in the grade of epithelialization and in the extent of inflammatory reaction in both techniques. These results suggest no significant advantage for hand-sewn or stapled anastomosis concerning the risks of stenosis or leakage.

Definitive one-stage emergency management of acute uncomplicated left colonic obstruction

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The management and outcome of acute uncomplicated large bowel obstruction has been reviewed in a district general hospital over a 2-year period.

A total of 19 patients (11 women and eight men) with a mean age of 69 (range 41–92) years were treated under the care of two consultant surgeons. Most of the operations (n = 13) were performed by registrars. The site of the obstruction (without any perforation or peritonitis) was the splenic flexure in two, descending colon in six, sigmoid colon in eight and rectum in two. The underlying pathology included carcinoma in 17 patients, stricture due to diverticular disease and pseudo-obstruction in the remaining two patients. A variety of procedures was carried out: colonic resection/bowel lavage/primary anastomosis in 12, extended right hemicolectomy in two, Hartmann's procedure in two, palliative bypass in two and caecostomy in one. One elderly patient (80 years) died within 30 days of operation because of fulminant bronchopneumonia. There was no perioperative morbidity, including the reversal of the two Hartmann's procedures.

Routine colostomy is no longer indicated in the treatment of left-sided large bowel obstruction. It is clear that resection and primary anastomosis should be the rule, and colostomy should be reserved for exceptional circumstances.

Clinical appraisal of solitary rectal ulceration

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This paper describes 89 patients with histologically proven solitary rectal ulceration. The mean age at onset of symptoms in men (n = 27) was 27 (range 13–61) years and in women (n = 62) 39 (range 15–82) years. The incidence was 3·1 new cases per million per year.

Typical symptoms included rectal bleeding in 92 per cent, passage of mucus (91 per cent), tenesmus (73 per cent), constipation (54 per cent), abdominal discomfort (64 per cent) and rectal discomfort (44 per cent). Attempts at defaecation averaged 3·3 times per day; 64 per cent of patients resorted to digitation to aid evacuation. Complete rectal prolapse featured in 25 per cent, intussusception to the anal verge in 14 per cent, occult rectal prolapse in 14 per cent and anterior mucosal prolapse in 20 per cent. Ulcers were solitary in 37 per cent and multiple in 20 per cent. Hyperaemic granular mucosa was demonstrated in 34 per cent and polypoid lesions in 9 per cent. The pathological lesions were situated between 4 and 14 cm (mean 7·6 cm) from the anal verge. Mean perineal descent on straining as recorded by perineometer was 2·7 (range 0·75–6·0) cm. Difficulty with balloon expulsion from the rectum was noted in 65 per cent.

Advice regarding symptomatic management and reassurance helped many patients. Two-thirds of patients benefited from a high-fibre diet. Abdominal rectopexy gave good results in patients with coexisting complete rectal prolapse but was less effective for mid-rectal intussusception.

Comparison between different faecal occult blood tests in neoplastic and inflammatory diseases of large bowel

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The preliminary results of a study in progress comparing three different faecal occult blood tests in patients with neoplastic or inflammatory bowel diseases or without any intestinal disease are presented.

A total of 65 patients with the following diagnoses entered the study: cancer (32), benign neoplasms (seven) chronic inflammatory diseases of the large bowel (seven), and control individuals (19). The patient's history and clinicopathological data were collected on admission. The diagnosis was confirmed by histological examination of colorectal tissue samples taken endoscopically or from the surgical specimen. After a meat-free diet for 3 days, three faecal samples were collected, frozen at −80°C and analysed by three different faecal occult blood tests: guaiac test (test on guaiac-impregnated paper); anti-Hb test (immunological test with monoclonal antihuman-Hb antibodies); and anti-Hb+anti-Tf test (immunological test with monoclonal antihuman-Hb and antihuman-transferrin antibodies). The sensitivity, specificity and predictive values of the three tests used were calculated.

In patients with cancer, the sensitivity rate was lower in the guaiac test than the anti-Hb or anti-Hb+anti-Tf tests; a high rate of false-negative results was observed in the guaiac test (40·6 per cent) as well as in the anti-Hb (21·9 per cent) and anti-Hb+anti-Tf (25 per cent) tests. In tumours staged early (within the muscle layer in six cases) the sensitivity was low (guaiac test 33·3 per cent; anti-Hb test 66·7 per cent; anti-Hb+anti-Tf test 50 per cent); in advanced tumours (beyond the muscle layer in 26 cases) the sensitivity was higher (guaiac test 65·4 per cent; anti-Hb test 80·8 per cent; anti-Hb+anti-Tf test 80·8 per cent), but gave a large number of misdiagnosed neoplasms (guaiac test, nine cases; anti-Hb test, five cases; anti-Hb+anti-Tf test, five cases). In patients with polyps and inflammatory disease, the sensitivity was very low in all three tests; in the control group, false-positive results were detected in only one, two and two cases by the guaiac, anti-Hb and anti-Hb+anti-Tf tests respectively. The specificity was high for all tests (guaiac test, 4·7 per cent; anti-Hb test, 89·5 per cent; anti-Hb+anti-Tf test, 89·5 per cent). The predictive value for overall disease was 95·8, 93·9, and 93·5 per cent for the guaiac test, anti-Hb test and anti-Hb+anti-Tf tests respectively. However, it was higher in the tumour group than in the polyp or inflammatory disease groups.

The large number of false-negative results in patients with tumour, polyps and inflammatory disease decreased the sensitivity for all tests used in the present study, particularly for tumours staged early. However, the specificity and predictive values of the tests were very high. The higher costs of the anti-Hb and anti-Hb+anti-Tf tests (six times more expensive) in comparison with the guaiac test suggest that, despite its limited sensitivity, the guaiac test is likely to remain the test of choice for mass screening because of its good specificity for tumours.

Skin-stapled colonic anastomosis: a workshop study

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The use of disposable skin staples for intestinal anastomosis was first described by Fackler during the Vietnam War. Animal studies have proved the technique to be fast and effective for small bowel anastomosis. If skin-stapled colonic anastomosis can be shown to be suitable for use under arduous battlefield conditions it would allow military surgeons to determine whether there are any indications for primary colonic repair in war.

A craft workshop study has been devised to determine the level of surgical skill required to perform an effective skin-stapled colonic anastomosis, having been introduced to the technique for the first time. This video presentation is the standardized teaching method of the craft workshop study. After a short introduction the author performs an unedited skin-stapled anastomosis on pig colon.

Preliminary results (n = 44) suggest skin-stapled colonic anastomosis is easily mastered by surgeons of all grades.

Ulcerative colitis: prospective surveillance and flow cytometric DNA analysis in an unselected population

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Between 1977 and 31 December 1991, 135 patients (of whom 57 had had total colitis for >10 years) were followed by clinical surveillance including colonoscopy with biopsies. DNA analysis was performed from 1984. A total of 38 patients left the study: nine died (one had colitis, one colonic carcinoma), 15 left because of radical operation and 14 for other reasons. Some 631 colonoscopies were performed. Four patients had colorectal carcinoma diagnosed. High-grade dysplasia was detected in five patients. Only two of these underwent operation because of dysplasia. Flow cytometric DNA analysis was performed in 102 patients with colitis for >6 years. DNA status was aneuploid in 17 patients, of whom 16 had total colitis. The results were reproducible at consecutive examinations and correlated well with dysplasia.

The risk of cancer or high-grade dysplasia was low, but surveillance was no guarantee against cancer or cancer death. Few operations were performed for imminent cancer, and the cost–benefit of the programme must be questioned. However, the follow-up provided reassurance and continuity, and gave possibilities to assess new cancer-predictive markers. DNA aneuploidy correlated well with other cancer risk factors, but its independent value as a cancer predictor remains to be established.

Ileal pouch–anal anastomosis for ulcerative colitis and familial adenomatous polyposis: requirement for endoanal mucosectomy

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Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is now an established surgical procedure for ulcerative colitis (UC) and familial adenomatous polyposis (FAP). However, whether to preserve the anal mucosa to enhance continence remains controversial. The aims of this study were to assess the clinical outcome after IPAA with mucosectomy for UC or FAP and to characterize the histology of the stripped anorectal mucosa.

From June 1986 to November 1992, 28 patients underwent IPAA with mucosectomy, 16 for UC (group 1) (nine men and seven women, mean age 30 years) and 12 for FAP (group 2) (eight men and four women, mean age 27 years). There were no intraoperative complications in group 1, but mucosectomy was difficult in ten patients and anastomosis performed under some degree of tension in ten. In group 2, there was a direct injury of the internal sphincter by a posterior tear during mucosal stripping in one case. Mucosectomy was easy to perform in eight patients and ten anastomoses were performed under tension. There were no postoperative complications directly related to the mucosectomy or anastomosis in either group.

Functional results were good, with normal continence in 80 per cent of patients with UC and 92 per cent of those with FAP. Histological examination of sections of the stripped anal mucosa in group 1 showed chronic active UC in eight patients, chronic non-active UC in four and quiescent UC in four. There was only one case of mild dysplasia in a patient with a Dukes' A carcinoma of the large bowel. In group 2, the anal mucosa showed micropolyps in all cases with mild dysplasia in three and moderate dysplasia in nine.

In conclusion, a careful mucosectomy does not affect the surgical outcome and functional results. Since removal of the diseased tissue is more complete, the anal mucosa should always be removed down to the level of the dentate line in restorative proctocolectomy for UC or FAP.

Colorectal cancer

Colorectal cancer in under 45-year-olds: prognostic factors and survival

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Over 1800 patients die each year in the Grampian region from colorectal cancer, 3 per cent of whom are in the under-45 years age group.

The records of 92 patients under 45 years with colorectal cancer were reviewed from the period 1970 to 1990. Ninety-one patients (44 men and 47 women) presenting with 35 rectal and 56 colonic tumours were evaluated. They were staged using tumour node metastasis (TNM), Dukes' and Jass classifications, and examined with reference to disease-free survival and overall survival. Formalin-fixed wax-embedded material (tumour and regional nodes) was examined microscopically for evidence of perineural, intramural and extramural vascular invasion. Univariate and multivariate Cox multiple hazard statistical analyses were performed to determine risk factors.

The overall 5-year and 10-year survival for all groups was 61 and 59 per cent respectively. Dukes' stage provided the best single measure of risk in all three outcome groups, outperforming the Jass classification (exponential coefficient (EC) 2·95, $P < 0\cdot0001$ Duke's *versus* EC 2·14, $P < 0\cdot0001$ Jass). Mucinous tumours were significantly more likely to recur locally (EC 4·92, $P = 0\cdot03$). M, N and presence of perineural tumour invasion were independently predictive of metastatic recurrence while T, N, M and extramural vascular invasion were predictive of overall survival. There was no evidence that requirement for emergency surgery influenced survival.

Few studies have provided detailed analysis of colorectal cancer in the under-45 group and these data furnish useful information on the risk factors and prognosis in this important subgroup.

Combined multimodality treatment of primary or recurrent locally advanced rectal cancer

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After surgery alone, locally advanced rectal cancer has a poor prognosis as the extent of local disease makes it impossible to perform a resection without leaving gross or microscopic residual disease. From January 1990, ten patients with primary (group 1, five cases) or recurrent (group 2, five cases) locally advanced rectal cancer, without evidence of distant metastases, underwent combined multimodality treatment of preoperative chemoradiotherapy (FUMIR; 24 Gy × 2), surgical resection, intraoperative radiotherapy (IORT) and postoperative chemotherapy (FUL × 9).

Surgery consisted of anterior resection in two patients, abdomino-perineal resection in seven, and resection of the recurrence *en bloc* with coccyx and sacrum (S4–S5 vertebrae) in one. IORT fields encompassed tumour bed (nine) or microscopic residual disease (one). Areas irradiated were the sacrum (five) or the sacrum and the lateral pelvis wall (five). The most frequently used cone sizes were 5 and 6·5 cm. IORT doses were 10 Gy (eight) and 15 Gy (two).

There were no postoperative mortalities or major complications. Two wound infections occurred. In group 1 after a mean follow-up of 10 (range 2–19) months all patients are alive and disease-free. In group 2 two patients are alive with lung metastases (without evidence of local failure) at 34 and 24 months; three patients are alive and disease free (at 24, 12 and 2 months respectively).

IORT, combined with external radiotherapy, in primary and locally recurrent advanced rectal cancer appears safe, tolerable and may result in good local control of disease.

Growth pattern of colorectal cancer: comparison of *in vitro* and *in vivo* carcinoembryonic antigen expression

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Carcinoembryonic antigen (CEA) has been used for monitoring early recurrence of colorectal cancer; however, it is not known whether sequential CEA determination may be a reliable indicator of tumour growth.

A cancer cell line (FA-18) of a hepatic metastasis was established from a 43-year-old woman who, 24 months earlier, underwent right hemicolectomy followed by 5-fluorouracil plus levamisole chemotherapy for Dukes' B cancer of the caecum. Clinical follow-up and CEA blood level tests were performed every 45 days until hepatic metastases were detected. The cancer cell line was maintained in standard culture conditions and growth curves (t_2 44 h, clonogenicity 0·6 per cent) were carried out for 15 days. Every 2 days, cells were counted and the CEA level determined in concomitant supernatant by the same method used for blood samples. *In vivo* and *in vitro* CEA levels and cell counts were plotted as ln (x) graphs. The slope of linear regression and the coefficient of correlation (R^2) were established for each graph using Statview 512^+ software. The slope of linear regression of the FA-18 growth curve and concomitant CEA expression curve were 0·3 and 0·4 respectively. The R^2 values of linear regression were >0·95. CEA blood level regression was linear with R^2 0·99 and slope 0·012.

Both cell growth and CEA expression curves of the FA-18 cell line were exponential and near parallel according to their regression slope and R^2 values. The CEA blood level curve was also exponential but the slope reduced compared with *in vitro* measurements. These results from a single tumour are of interest and merit investigation in larger series.

Oncoscint-Cyt 103 is helpful in the localization of primary and secondary colorectal carcinoma

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Oncoscint-Cyt 103 is an indium-111-labelled radiopharmaceutical agent employing the immunoglobulin G murine monoclonal antibody B72.3 raised against the TAG-72 antigen expressed on 95 per cent of colorectal cancer cells. Experience is reported with the first 20 scans of patients who were screened after the diagnosis of colorectal carcinoma was made, who were scanned because of a high suspicion of the disease or who were scanned in follow-up after treatment of colorectal cancer. Analysis of results indicates that the method has a sensitivity of 69 per cent with a specificity of 86 per cent (mixed primary and secondary disease). The scan is useful even when the TAG-72 antigen is not measured and other tumour markers can be assayed to select patients for scanning. Primary tumours of each Dukes' stage can be detected. Whole-body scans can be acquired without increasing radiation dose, which may be helpful in selecting patients for re-resection (by excluding extra-abdominal disease). Although experience with the scan is at an early stage, the potential for detection of disease is shown. In particular, the scan may be helpful in detection of disease in the pelvis, where diagnosis by conventional techniques has been problematical.

Excision of rectal tumours using transanal endoscopic microsurgery

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Upper rectal tumours are traditionally excised by low anterior, presacral or trans-sphincteric resection. Transanal endoscopic microsurgery (TEM) is a minimally invasive technique utilizing three-dimensional optics and an operating proctoscope. Insufflation, irrigation and suction are provided by an endosurgical unit connected to ports in the proctoscope. Either full-thickness or submucosal resection can be performed using a high-frequency knife. The wound is then sutured with silver clips instead of knots. Seven patients (two men, five women) have so far undergone TEM for upper rectal tumours. The mean age of the patients was 67 years and the mean distance of the tumour from the anal margin 12 cm. Of the tumours, six were tubular villous adenomas and one was a carcinoma (T_1). All were completely excised with a mean resection margin of 0·75 cm. The median diameter of the lesions was 3·2 cm. The mean operating time was 80 min and the mean postoperative hospital stay 4 days. These data suggest that TEM provides a safe, minimally invasive alternative technique for the treatment of upper rectal tumours.

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Interleukin 2 therapy of colorectal carcinoma: prediction of response and survival

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The response and natural history of 24 patients with metastatic colorectal cancer was studied following treatment with recombinant interleukin 2 (rIL-2). rIL-2 was given by continuous intravenous infusion (750 kIU m^{-2} h^{-1} for 120 h), followed by injections of 5-fluorouracil (600 mg m^{-2}) and leucovorin (folinic acid; 25 mg m^{-2}) at weekly intervals for 3 weeks. Patients were stratified by the basal serum levels of acute-phase proteins (C-reactive protein (CRP), α_1-antitrypsin, retinol-binding protein (RBP), transferrin (TF), albumin) and tumour markers (carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9)). Numbers of responders *versus* non-responders and of those surviving more than *versus* less than 1 year were compared by Fisher's exact test (two-tailed). Failure of response to treatment occurred when CRP was < 10 mg l^{-1} ($P < 0\cdot0003$), albumin < 37 g l^{-1} ($P < 0\cdot01$) and CEA > 30 ng ml^{-1} ($P < 0\cdot003$). Reduced survival (< 1 year) following treatment occurred when CRP was > 10 mg l^{-1} ($P < 0\cdot05$), α_1-antitrypsin > 2·2 g l^{-1} ($P < 0\cdot005$), albumin < 37 g l^{-1} ($P < 0\cdot01$) and CEA > 30 ng ml^{-1} ($P < 0\cdot05$).

These results suggest that abnormal acute phase and tumour markers before treatment are associated with a low response rate and poorer overall survival.

Primary squamous cell carcinoma of the colon and rectum: report of two cases

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Squamous cell carcinoma represents the most frequent malignant tumour of the anal canal but accounts for only about 0·1 per cent of all primary malignancies of the colon and rectum. To date, only 72 squamous cell or adenosquamous carcinomas have been reported at this site. Over the past 15 years, the authors have observed two patients with this condition. Neither had had a previous cancer. In one patient the tumour was localized in the ascending colon with simultaneous hepatic metastases. The patient underwent right hemicolectomy followed by chemotherapy, but died 5 months later from hepatic failure. In the second patient the tumour was localized in the rectum without evidence of metastases. This patient was operated on recently and is currently undergoing radiotherapy. The diagnosis of primary squamous cell carcinoma of the colon and rectum is valid if another primary site or continuity with the stratum germinativum epidermidis (Malpighii) have been excluded. The prognosis compared with colorectal adenocarcinoma appears to be worse.

Low-dose preoperative radiotherapy for rectal cancer: a prospective randomized trial

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A prospective randomized trial of preoperative radiotherapy (three 50 cGy fractions over 5 days) followed by surgery (group 1) within 2 days *versus* surgery alone (group 2) was carried out in patients with rectal cancer 12 cm from the anal verge. A total of 27 surgeons from 15 centres in England entered patients who were followed to death or for a minimum of 5 years. Local recurrence was documented.

Of the 478 patients randomized between 1980 and 1984, 468 (mean age 66 (range 31–94) years, 273 men, 195 women) met the entry criteria (group 1, 228; group 2, 239). Of the 410 (group 1, 196; group 2, 214) who had all the primary disease excised, 310 (group 1, 154; group 2, 156) had curative operations. In all, 31 patients (7 per cent) died in the perioperative period (group 1, 21 (9 per cent); group 2, ten (4 per cent); $P < 0\cdot05$). Cardiovascular and thromboembolic complications were more common in group 1 (group 1, 30 *versus* group 2, eight; $P < 0\cdot005$). Of the patients who had curative operations, 157 (50 per cent) (group 1, 76 (49 per cent) *versus* group 2, 80 (51 per cent); P not significant) survived 5 years. Local treatment failure was documented at follow-up in 82 patients (group 1, 31 *versus* group 2, 51; log rank test $\chi^2 = 4\cdot37$, $P < 0\cdot05$). After curative resections, 70 patients developed recurrent disease that in 33 was due to local treatment failure (group 1, 11 *versus* group 2, 22; log rank $\chi^2 = 3\cdot59$, $P = 0\cdot058$).

Low-dose preoperative radiotherapy did not influence 5-year survival but resulted in a decrease in local treatment failure, and an increase in perioperative morbidity and mortality rates.

Accuracy of endosonography in the staging of rectal cancer before and after preoperative radiotherapy

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Between January 1988 and August 1992, 55 patients with rectal cancer were evaluated by clinical staging and endorectal sonography before (52 patients) and after (50) preoperative radiotherapy. Two criteria were correlated with histological findings: confinement to the rectal wall or spread beyond and uT stage; and the presence of mesorectal lymph node involvement.

The 52 patients who underwent endorectal sonography before radiotherapy were staged as uT$_2$ (seven patients), uT$_3$ (41) and uT$_4$ (four). At 15 days after irradiation, endorectal sonography showed a regression of the tumour in all patients; the uT stage was different in 19 patients and the uN stage was different in ten. Comparison of the preoperative and postoperative sonographic assessment of local invasion beyond the rectal wall with postoperative histopathology revealed a correlation with endorectal sonography before irradiation in 31 of the 52 staged tumours (60 per cent), and with sonography after irradiation in 34 of the 50 staged tumours (68 per cent). The presence of mesorectal lymph node involvement determined by histological examination correlated with the results of endorectal sonography after radiotherapy for 33 of the 49 staged tumours (67 per cent).

Endorectal sonography provides a good assessment of tumour stage before irradiation. Radiotherapy altered endosonographic staging of rectal cancer and downstaging occurred in 22 per cent of patients.

Carcinoma of the rectum: role of mesorectectomy in the early postoperative course

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A total of 573 patients with rectal carcinoma were operated on from January 1985 to December 1991. The age range was 17–86 years. There were 42 per cent women and 58 per cent men. Mesorectectomy was performed in 376 patients. There were no statistically significant differences in age, sex and tumour characteristics between groups of patients that did or did not undergo mesorectectomy. Mesorectectomy did not extend the operating time or cause greater perioperative blood loss. The postoperative specific morbidity rate in patients who underwent mesorectectomy was 6·7 per cent (25 patients). The most frequent complication was postoperative fistula, which affected 15 (4·0 per cent) patients. Seven (1·9 per cent) patients had peritonitis, one testicular necrosis, one sepsis and one postoperative bleeding. The postoperative non-specific morbidity rate was 4·5 per cent (17 patients). Nine patients had urinary infection and five myocardial infarction; testicular necrosis, sepsis, postoperative bleeding, stroke and pulmonary embolism were seen as single complications. The mortality rate was 4·3 per cent. The mean hospital stay was 20·2 (median 18) days. There were no statistically significant differences in mortality, morbidity and hospital stay between the groups of patients that did or did not undergo mesorectectomy. It is concluded that operative procedures that include mesorectectomy do not have negative effects on the early postoperative course.

Venous invasion in colorectal carcinoma

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The presence of venous invasion in colorectal carcinoma is known to be associated with poor survival. In an attempt to clarify the mechanisms underlying this prognostic influence a systematic study was undertaken of venous invasion in 294 cases of colorectal carcinoma of a series of 353 cases submitted for resection from 1960 to 1991. Venous invasion was detected in the histological sections of 212 cases (72·1 per cent) using haematoxylin–eosin and orcein stain for elastic tissues. A significant association of venous invasion was found with right colon localization ($P = 0{\cdot}026$), ulcerative and/or infiltrative growth ($P = 0{\cdot}007$), poor differentiation ($P = 0{\cdot}0001$), lymphatic permeation ($P = 0{\cdot}001$) and stage C of Dukes' classification ($P = 0{\cdot}0001$). Preoperative carcinoembryonic antigen levels were found to be significantly higher in patients with carcinoma displaying venous invasion. No correlation was observed between the presence of venous invasion and sex or age of patients, intestinal obstruction and size of tumours.

It is concluded that the prognostic influence of venous invasion cannot be properly evaluated without taking into consideration the other biological parameters that are closely associated with the aggressiveness of neoplastic cells.

Cancer of the sigmoid colon and rectum: stapling techniques for anastomosis below the peritoneal reflection

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Two stapling techniques used in colorectal surgery were compared. Anastomosis was perfomed in all cases below the peritoneal reflection.

A total of 31 patients suffering from cancer of the rectum or sigmoid colon were operated on in the past 18 months. Some surgeons perfomed the anastomosis by means of circular stapling (CS) and others selected the Roticulator (R) plus CS. Because of an obstructing tumour or a narrow pelvis, defunctioning colostomy was performed in some cases.

	CS (n = 12)	R plus CS (n = 19)
Mean(s.d.) age (years)	70·4(5·5)	67·7(12·6)
Mean(s.d.) hospital stay (days)	12·2(4·0)	12·1(5·0)
Rectum	9 (75)	15 (79)
Sigmoid colon	3 (25)	6 (32)
Dukes' stage		
A	3 (25)	4 (21)
B	4 (33)	7 (37)
C	4 (33)	8 (42)
'D'	1 (8)	0 (0)
Distance*		
<1 cm	0 (0)	2 (11)
1–2 cm	3 (25)	5 (26)
>2 cm	9 (75)	12 (63)
Lateral colostomy	3 (25)	6 (32)
Infection	1 (8)	1 (5)
Leak	0 (0)	1 (5)
Mortality	0 (0)	0 (0)

Values in parentheses are percentages. *Distance from tumour to resection line. *P* not significant for all parameters

In conclusion, both techniques are safe and have similar postoperative results. The distance between the tumour and line of resection was similar with the CS or CS plus Roticulator technique.

Audit of rectal cancer surgery: outcome in a defined population over 23 years

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All patients with carcinoma of the rectum or rectosigmoid junction who at the time of diagnosis lived within the catchment area of Motala hospital (87 000 inhabitants) were studied. Data were checked with the population register and the regional cancer register. Data of patient history, operation, histopathology and follow-up were collected retrospectively from 1 January 1970 to 31 December 1983, and prospectively thereafter. Actuarial methods were used for calculation of crude mortality rate, mortality rate with cancer (systemic and/or local) and mortality rate with local recurrence. Nine patients received preoperative radiotherapy within the framework of a nationwide controlled study. Since January 1990 all patients with low and mid-rectal tumours were treated by total mesorectal excision (TME).

Between 1970 and 1989, 332 patients were treated, 216 (65 per cent) with curative intent. Of those patients who underwent abdominal tumour resection, 21 per cent had anterior resection (AR) in the period 1970–1979, and 51 per cent in the period 1980–1989. For curative resections the mortality rate from generalized cancer after 5 and 10 years was 41 per cent and 50 per cent, respectively, and mortality rate from local recurrence was 33 per cent and 41 per cent. There was no difference in mortality rates between the two decades. Inadvertent opening of the rectum during the operation doubled the local recurrence rate. From 1 January 1990 to 31 December 1992, 46 patients were treated, 33 with curative intent. Of 33 patients with abdominal tumour resection, 24 underwent AR. Three curatively treated patients have died with manifestations of cancer, two with cerebral metastases and one with a local recurrence.

In conclusion, these results show that local recurrence rate during the pre-TME period (1970–1989) was high. Initial results with TME are promising. Audit is necessary for rectal cancer surgery.

Risk factors for local recurrence after radical surgery for rectal carcinoma: a prospective multicentre study

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Local recurrence after radical surgery for rectal carcinoma is highly debilitating and, in most cases, fatal. Recurrence rates vary widely in published studies. To identify risk factors for local recurrence in an unselected population and to evaluate methods for identification of local recurrence at a resectable stage, a multicentre prospective study comprising 41 Norwegian hospitals was arranged by The Norwegian Cancer Registry.

During a 2-year period ending in August 1988, 284 patients aged less than 75 years with radically resected rectal carcinoma were entered into the study. Patients were followed at 3-monthly intervals for 2 years, and later at 6-monthly intervals. Follow-up included clinical examination, ultrasonography of the liver, and determination of serum levels of carcinoembryonic antigen. At predetermined intervals patients were examined by colonoscopy and chest radiography.

At a median observation time of 60 (range 48–72) months, complete data were available on 275 patients. Local recurrence was diagnosed in 81 patients (29 per cent), including 69 with no evidence of distant metastases. Radical re-resections were performed in 26 patients (38 per cent) without distant spread. Possible risk factors for local recurrence were studied in a multivariate analysis (logistic regression): age, sex, Dukes' stage, type of hospital (local, district, university), tumour distance from the anal verge, divided in three groups (lower, 0–5 cm; middle, 5–10 cm; upper, ≥11 cm), and resection method (local excision, abdominoperineal resection (APR), anterior resection). Only distance from the anal verge ($P = 0{\cdot}02$) and resection method ($P < 0{\cdot}02$) were significant risk factors for local recurrence. Tumours in the middle and lower part of the rectum recurred more frequently (middle, 32 of 86, 37 per cent; lower, 25 of 81, 31 per cent) than in the upper rectum (23 of 108, 21 per cent), irrespective of Dukes' stage. When compared with tumours removed by local resection, cancers treated with anterior resection had fewer recurrences (odds ratio 0·52 (95 per cent confidence interval 0·35–0·76)). APR carried the lowest risk of recurrence (odds ratio 0·36 (95 per cent confidence interval 0·25–0·52)).

A high local recurrence rate in the lower two-thirds of the rectum, irrespective of tumour stage, may indicate that technical factors related to the surgical procedure are more important than tumour stage.

Patterns of recurrence following surgery for carcinoma of the colon and rectum

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Factors influencing recurrence in colorectal cancer remain under debate. To investigate which factors were related to locoregional or distant recurrence of colorectal carcinoma, a series of 408 patients with colorectal carcinoma who underwent surgical resection for cure between 1979 and 1988 was studied. The median (range) follow-up period was 7·6 (4–14) years. Recurrence was diagnosed by clinical, radiological, endoscopic and/or histological features in 186 patients (45·6 per cent), while 222 (54·4 per cent) remained free from disease at the end of the follow-up period. Locoregional recurrence was seen in 137 patients (33·6 per cent of the global series), and distant recurrence in 99 patients (24·3 per cent). Fifty patients showed both types of recurrence simultaneously.

The following factors were found to be statistically related to locoregional recurrence: rectal location, level of invasion of the intestinal wall, lymph node involvement and blood transfusion. Distant recurrence was related to complete circumferential involvement of the colonic wall, level of invasion of the intestinal wall, lymph node involvement and blood transfusion. Age, sex, tumour size, duration of symptoms, surgical technique in the left colon (segmented colectomy *versus* standard hemicolectomy) and in the rectum (anterior resection *versus* Miles' operation), and surgical margins in rectal cancer had no influence on patterns of recurrence.

Multivariant analysis of prognostic factors in colorectal carcinoma: an approach to a new prognostic classification

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Dukes' classification is of widespread use in the prognostic evaluation of patients with colorectal cancer. Nevertheless this classification has some limitations, basically when classifying just a small group of patients as 'good prognosis'.

Factors influencing survival were studied in a series of 410 patients who underwent surgical resection for cure from a global group of 689 patients with colorectal cancer treated from 1979 to 1988. Analysis was by means of a multivariate Cox regression model using 14 clinical, analytical and histological variables. It was found that localization of the tumour, presence of obstruction or perforation, level of invasion of intestinal wall, lymphatic involvement, grade of cellular differentiation and timing of blood transfusion were statistically related to prognosis.

With these variables a classification into three groups with different prognoses could be established: group 1 ($n = 135$), 5-year survival rate 84 per cent; group 2 ($n = 124$), 5-year survival rate 50 per cent; and group 3 ($n = 151$), 5-year survival rate 20 per cent.

In a second phase of the study, this classification was used prospectively in a series of 70 patients who underwent surgical treatment of colorectal cancer in 1989 (follow-up 4 years) and showed a good correlation between expected and actual prognosis. From these results, it is believed that a more accurate prognosis can be made in surgically treated colorectal carcinoma by considering variables other than those used in Dukes' classification alone.

Results of extended resection for colonic cancer adherent to other organs

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Carcinoma of the colon can occasionally adhere to other organs. In this situation it has been policy, whenever possible, to perform an extended resection with curative intent. The aims of this study were to evaluate whether this surgical procedure is justified, in terms of the postoperative morbidity and mortality rates.

From 1985 to 1990, 172 patients with colonic cancer were operated on. The mean age was 62 (range 38–82) years. In 38 patients (22 per cent) the tumour was adherent to other organs; of these, 23 were treated by an extended *en bloc* resection with curative intent, the other 15 undergoing palliative surgery. The postoperative morbidity and mortality rates in the *en bloc* resection group were 30 per cent (seven cases) and 9 per cent (two cases) respectively. The 5-year survival rate was 28 per cent; the mean survival of the palliative group was 7 months. Results of this study suggest that colonic cancer involving adjacent structures should not preclude a surgical procedure with curative intent.

Effect of essential fatty acids on natural cytotoxicity in patients with colorectal cancer

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Essential fatty acids (EFAs) have been shown to modulate lymphocyte reactivity and destroy tumour cells *in vitro*. Natural cytotoxicity, mediated by natural killer (NK) and lymphokine-activated killer (LAK) cells, is believed to have an important anticancer role *in vivo*. The effect of EFAs, given orally, on NK and LAK cell activity in patients with both localized (seven cases) and advanced (11) colorectal cancer, was studied.

Activity of effector cells was expressed as lytic units, using *in vitro* ^{51}Cr release assays: NK (K562), LAK (DAUDI). NK cell activity was unchanged after 15 days' treatment with EFAs in both groups, but was significantly reduced after 1 ($P < 0{\cdot}05$) and 2 ($P < 0{\cdot}01$) months' supplementation (advanced group). LAK cell responses showed no alteration after 15 days' treatment with EFAs (both groups) but the cytolytic activity on prolonged intake (1 and 2 months) showed an overall reduction (not statistically significant). Cell surface marker analysis revealed reduced absolute numbers of CD16$^+$ and CD57$^+$ lymphocytes in the localized group. Prolonged supplementation with high doses of EFAs may have detrimental effects on natural cytotoxic mechanisms.

Modulation of cytokine production by dietary essential fatty acids in patients with colorectal cancer

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Cytokines play a key role in the inter-relationships between nutrition, host defences and diseases. The effects of the essential fatty acids (EFAs) γ-linolenic acid (GLA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), 4·8 g day^{-1}, given in combination as dietary supplementation, on cytokine production was investigated in patients with colorectal cancer. Total levels of serum cytokines – interleukins (IL-1β, IL-2, IL-4, IL-6), tumour necrosis factor (TNF) α and interferon-γ (IFN-γ) – were analysed using the enzyme-linked immunosorbent assay (ELISA) technique at different time intervals during the course of treatment.

Fatty acid uptake and patient compliance were confirmed by a significant increase in levels of GLA, EPA and DHA in all the three fractions (triglyceride, cholesterol and phospholipid). There was no significant alteration of total serum cytokine production in the first 2 months of EFA ingestion in both the localized and advanced groups, but the levels of serum cytokines steadily declined after 2 months and continued to fall, reaching minimum levels at 6 months, after EFA supplementation. EFAs at the doses used in this study reduced total IL-1β synthesis by 61 per cent ($P = 0{\cdot}044$), IL-2 by 63 per cent ($P = 0{\cdot}05$), IL-4 by 69 per cent ($P = 0{\cdot}025$), IL-6 by 83 per cent ($P = 0{\cdot}03$), TNF-α by 73 per cent ($P = 0{\cdot}04$) and IFN-γ by 67 per cent ($P = 0{\cdot}05$).

The present study has shown that long term n-3 and n-6 EFA treatment reduced cytokine production. Although their induced reduction may have beneficial anti-inflammatory effects, the suppression of IL-1β, IL-2 and IFN-γ production may not be desirable in malignant disease.

Variation in receptor status between primary colorectal cancer and liver metastases

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Measurement of oestrogen receptor (ER) and progesterone receptor (PR) levels in the cytosol fraction of tumour homogenates is a routine procedure in evaluation of breast cancer treatment. The receptor status of primary colorectal cancer has also been investigated. However, there is no information on changes in receptor level and status during the clinical course of colorectal cancer. A prospective follow-up study was carried out including 61 patients over a 3-year period, to detect any influence of hormonal status on prognosis and metastatic pattern of colorectal cancer. ER and PR levels were measured in 60 colorectal cancers, giving mean(s.e.m.) values of 12·5(24·9) and 0·7(3·6) fmol per mg protein respectively. Of the colorectal cancers 60 per cent are ER-positive and 5 per cent are PR-positive. Fifteen liver metastases were also resected or biopsied during the study. ER and PR levels were measured, giving respectively a mean(s.e.m.) value of 21(19) and 202(221) fmol per mg protein. Of the metastases 73 per cent are ER-positive and 80 per cent are PR-positive. The statistical significance is low for ER ($P < 0{\cdot}10$) but very high for PR level and status ($P < 10^{-7}$), when comparing colorectal cancer and metastases. For comparison, the ER and PR levels in liver metastases of colorectal cancer are respectively 17 and 172 per cent of the levels found in primary breast cancer treated during the same period of time. The presence of PR in liver metastases of colorectal cancer and not in primary colorectal cancer may be a marker of the clone of cancer cells that are able to produce metastatic deposits in the liver. It may also be induced by an autocrine or paracrine effect between the metastatic cells ('seed') and the liver ('soil'). It is suggested that there should be a European trial with adjuvant hormonal manipulation of PR in patients with colorectal cancer.

Management of colorectal cancer

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From January 1985 to December 1990, 591 patients underwent operation for colorectal cancer. There were 325 men and 266 women. The average age was 70 (range 33–93) years. The more important symptoms were abdominal pain (35 per cent) and diarrhoea (30 per cent). Diagnosis used blood (carcinoembryonic antigen) and urine analysis, enema and colonoscopy with biopsy. The rectum is the commonest site of these tumours (212). Elective surgery was performed in 458 patients. Preoperative preparations included oral solutions (polyethylene glycol), enemas, antibiotics and anticoagulation prophylaxis. In emergency surgery on 133 patients, antibiotics and, in 35 cases, anterograde lavage were employed. Mechanical sutures were used in more than 90 per cent of anastomoses.

Resection was performed in 537 patients, with anastomoses in 389 cases, and without in 148. The techniques used most often were anterior resection (155 patients), right hemicolectomy (90), sigmoidectomy (88) and Hartmann's (84). Overall, 188 patients had postoperative complications, with the majority after emergency surgery. Local complications were more frequent than general, with wound abscess (88 patients) and anastomotic leak (36). Reoperation was performed in 35 patients, in ten cases for leakage. The mortality rate was 35 patients, 24 after emergency surgery.

Sequential anterior–posterior resection with coloanal anastomosis for distal rectal tumours

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Sequential anterior–posterior resection of the rectum was developed: (1) for resection of tumours in the distal third of the rectum and; (2) to improve in-continuity resection of perirectal fat in its inferior and lateral extent into which spread of tumour may occur.

Between 1988 and 1992, 15 patients were selected for operation. Preoperative evaluation included endoscopy, computed tomography of the pelvis and carcinoembryonic antigen evaluation. Initial low anterior dissection was followed by a posterior transcoccygeal (Kocher) approach to the distal rectum. Transection of the external but not the internal anal sphincter aided dissection in the intersphincteric plane and tissues circumferentially to the rectum. The intact internal sphincter facilitated the creation of a coloanal anastomosis.

Twelve patients had carcinoma of the rectum and three giant or recurrent villous adenoma. Two patients had tumour recurrence at 6 and 14 months that required abdominoperineal resection. Two other patients had terminal pulmonary metastases but no liver or local recurrence. Two patients developed strictures which responded to dilatation. All patients are continent with 0–5 motions per day. Eleven patients who would otherwise have had an abdominoperineal resection are now well without a colostomy.

It is concluded that the operation is an appropriate treatment in certain cases of tumour of the distal rectum and avoids a permanent colostomy.

Role of conservative treatment for low rectal cancer

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Transanal excision of low rectal cancer has long been reserved for patients unfit for major surgery. The development of preoperative diagnostic tools such as endorectal ultrasonography, which provides a precise assessment of depth of the intramural invasion of the tumour, together with the progress of pelvic and endocavitary radiotherapy, which allows a good local control of the residual disease, has recently changed the indications for conservative treatment of low rectal cancer.

From 1987 to 1990, eight patients with non-high-grade invasive rectal cancer were treated by full-thickness transanal excision as a curative procedure. Three patients had T_1 and five had T_2 cancers (four T_{2a} and one T_{2b}, i.e. infiltrating the muscularis propria). T_1 cancers were only excised, whereas T_2 cancers were treated by local excision and radiotherapy. Resection margins were disease-free. Mean follow-up was 2 years. All patients are alive with no sign of local recurrence.

Low, well or moderately well differentiated tumours, with no distant spread, extending no deeper than superficial layers of muscularis propria can be managed conservatively, providing that strict endoscopic and endosonographic postoperative surveillance is undertaken. Radiotherapy for T_1 cancers is still debated.

Conservative treatment by local excision and radiotherapy might have a role in the treatment of T_1 and T_2 low rectal cancer.

Monoclonal antibody imaging in surgical management of colorectal carcinoma

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Experience with the introduction of a new diagnostic method in oncosurgery is presented. Immunoscintigraphic use of radiolabelled monoclonal antibodies specifically targets tumour-associated antigens and seeks recurrent foci, metastases and primary tumours of colorectal carcinoma, facilitating their detection.

A commercial kit containing monoclonal antibodies radiolabelled with technetium-99 and indium-111 was used. Scintigrams were obtained by planar or single photon emission computed tomography scanning at two time intervals after administration of the radiolabelled drug. Since 1991, 50 immunoscintigraphic examinations of patients with colorectal carcinoma undergoing surgery were performed. The sensitivity attained was 84 per cent.

Immunoscintigraphy is a valuable complementary examination; it is a safe, non-invasive test that can be used for detection and presurgical staging of colorectal carcinoma and may play a significant role in follow-up in oncosurgery.

Intra-arterial chemotherapy for colorectal liver metastases using a totally implantable pump

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Intra-arterial chemotherapy shows significantly higher response rates than systemic chemotherapy, but the impact on survival and extrahepatic disease is unclear. In this trial, the possibility of increasing the response rate in patients with irresectable liver metastases but no extrahepatic disease was analysed. Patients were treated with intra-arterial floxuridine

0·25 mg kg^{-1} over 14 days via a totally implanted infusion pump with the addition of systemic folinic acid (100 mg m^{-2} day^{-1} over 4 days) and 5-fluorouracil (5-FU) 400 mg m^{-2} day^{-1} over 4 days. There were no postoperative complications. Fifteen of 18 patients have been evaluated; the median extent of liver involvement was 30 per cent. A complete response was achieved in seven patients, a partial response in three and no change in four. The overall response rate was thus 66 per cent; 57 per cent of patients are alive at 2 years. Thirteen of 17 patients developed chemically reversible hepatitis and four diarrhoea; there was neither biliary sclerosis nor gastric ulcer. Patient acceptance was excellent. These preliminary data suggest that a combination of intra-arterial floxuridine via an implanted pump and systemic 5-FU and folinic acid may reduce extrahepatic progressive disease without unacceptable toxicity.

Preoperative and postoperative penile rigidity in patients suffering from colorectal neoplasia

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Nocturnal penile tumescence and rigidity monitoring (NPTRM) is currently used to study patients who complain of sexual dysfunction. NPTRM is performed by computerized devices and helps to differentiate between organic and psychogenic impotence. This technique has been used to study 51 patients who underwent operation for colorectal cancer. NPTRM was performed for 2 consecutive nights before and after the surgical treatment. All subjects who complained of postsurgical sexual dysfunction underwent a multidisciplinary evaluation that included a sexual questionnaire. NPTRM, real-time monitoring of penile response to intracavernous injection of 20 µg prostaglandin E_1 and both vascular functional and neurological studies were undertaken. All these parameters were studied to determine whether NPTRM is a useful method of distinguishing postsurgical psychogenic impotence from that of post-operative organic causes.

Epidemiological and clinical considerations on right colonic cancer

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This retrospective study included 389 consecutive patients treated at this institution from 1983 to 1991. Of these, 81 patients had right colonic cancer: 36 (44 per cent) men and 45 (56 per cent) women, mean age (range) 67·6 (35–92) years. Right hemicolectomy and ileotransverse anastomosis was performed in almost all patients, whereas palliative bypass was performed in only one. Simultaneous cholecystectomy was performed in 13 cases (16 per cent). Operative mortality rate was 5 per cent. Clinical anastomotic leakage occurred in two patients (2 per cent). Patients treated as emergencies had similar morbidity and mortality rates to elective cases. The mean hospital stay was 10 days. Right colonic cancer had a higher incidence in women (55 per cent) than left colonic (47 per cent) or rectal (47 per cent) cancer. The incidence of right colonic cancer was greater in this series (1983–1991) (26·2 per cent) than in 1968–1982 (21·7 per cent). Coexistence of gallstones was noticed in only 4 per cent of patients with sigmoid and rectal cancer. Further epidemiological studies could document any trends in age, sex and anatomical distribution of colonic cancer.

Duodenum and small bowel

Indications for the Roux-en-Y jejunal loop in intestinal surgery

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This study aims to present the advantages of diversion or reconstruction using a Y loop in digestive and biliary surgery. A series is reported of 33 patients (20 men and 13 women, aged 27–80 years), operated on during the past 9 years. A Y jejunal loop was used in 19 patients for the following indications: conversion of anastomosis in patients with gastroduodenal or gastrojejunal anastomotic fistula (three cases); after gastric resection in patients with duodenal ulcer and duodenal diverticula (three); after exclusion of a postbulbar bleeding ulcer with *in situ* haemostasis (one); after excision of ulcer with precarious duodenal closure (three); closure of high-flow duodenal fistula (two); in patients with penetrating, bleeding duodenal ulcers with isolation of the papilla and bile duct after duodenal closure (two); for biliary obstruction by carcinoma of the liver and bile duct (two); and in complex biliodigestive fistula (three).

The advantages of this method include avoidance of reflux and stasis in afferent loops due to intestinal peristalsis, and preservation of a good anastomosis due to rich jejunal vascularization.

The results were good, with only one death after surgery in a patient with postoperative pancreatitis.

In conclusion, it is considered that the Roux-en-Y jejunal loop has a role in preventing some postoperative complications of gastroduodenal surgery.

Captopril increases endothelin release after small intestine ischaemia–reperfusion injury in the rat

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Captopril, unlike other angiotensin-converting enzyme (ACE) inhibitors, contains a sulphydryl group and can act as a free radical scavenger. Iloprost (ZK 36374) is a synthetic analogue of prostacyclin. This study was undertaken to investigate the effects of iloprost and captopril on small intestinal ischaemia–reperfusion injury in the rat. Experimental groups consisted of sham ($n = 6$), control ($n = 7$), iloprost ($n = 7$), captopril ($n = 8$), and captopril plus iloprost ($n = 8$). Superior mesenteric occlusion for 30 min was followed by 90 min reperfusion; portal venous blood was obtained for endothelin assay and ileal tissue samples were obtained for malonyldialdehyde (MDA), PGE_2 and leukotriene C_4 (LTC_4) determinations. MDA levels were reduced in rats receiving iloprost, captopril or both, indicating the inhibition of lipid peroxidation. Endothelin levels increased in the control group and this increase was reversed with iloprost. In the captopril group, endothelin levels were significantly increased and this was not reversed with the addition of iloprost ($t = 44·4$, $P = 0·000001$ and $t = 46·7$, $P = 0·000001$). LTC_4 levels were unchanged and PGE_2 levels were significantly reduced in the iloprost group. This study reveals that captopril increases the release of endothelin after small intestinal ischaemia–reperfusion injury and that this increase is unrelated to the arachidonic acid cascade.

Skin stapler intestinal anastomosis: a safe and efficient method in humans

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A reliable method of anastomosis of human intestine using an economical skin stapling gun has been used in 22 humans with various pathological conditions. The method is learned quickly and easily, is efficient in time (less than 10 min) and is inexpensive (£10).

Twenty-two patients with conditions including intestinal obstruction, neoplasia, chronic inflammatory disease, soiling and sepsis have demonstrated no contraindication to the method after resection of the diseased bowel. There have been no complications. Gross discrepancy in bowel size and contracted bowel in patients with epidural anaesthesia militate against the method.

This simple method now applied to human disease may be transferrable to laparoscopic intraperitoneal intestinal anastomosis.

Primary adenocarcinoma of the small intestine: 80 cases

French Association for Surgical Research and A. Fingerhut, M. Veyrieres, J.-M. Hay and H. Levard, *Bois Colombes, France*

Primary adenocarcinoma of the small intestine is rare, occurring in 0·5–5 per 1000 tumours of the intestinal tract. During the past 10 years 80 patients from 72 institutions have been studied retrospectively to analyse diagnostic, pathological and prognostic data. Intestinal obstruction was the single most common presentation (50 per cent of patients), followed by declining general health (45 per cent), abdominal pain (43 per cent), and anaemia (41 per cent). Nearly 33 per cent of patients were operated on as an emergency; 16 per cent of tumours were discovered only at exploratory laparotomy. Loss of weight, pain and anaemia were more common when the tumour was located in the proximal intestine. Intestinal obstruction was more common when the tumour was ileal.

Barium follow-through was the essential preoperative diagnostic tool, being positive in 82 per cent of patients. Some 92 per cent patients had a single tumour, 11 per cent had metastatic deposits and nearly 20 per cent had spread to adjacent organs at the time of surgery. The resectability rate of the tumours was 95 per cent; colonic resection was necessary in one-fifth of cases.

Operative mortality and morbidity rates were 13 and 33 per cent, respectively. Mortality and morbidity rates were significantly higher ($P < 0·01$) when the tumour was ileal and operated on as an emergency. Serosal involvement (80 per cent), lymph node involvement (52 per cent), and undifferentiated tumours (40 per cent) were associated with a poorer prognosis (P not significant). Villous adenoma (one case), colonic polyps (five), Crohn's disease (three) and carcinoma (ten) were associated in 15 per cent of patients. The overall cumulative survival rate was 35 per cent at 5 years. The survival rate was >50 per cent in the absence of serosal or lymph node involvement.

In conclusion, the prognosis in primary adenocarcinoma of the small intestine is not always poor. The essential need is to improve diagnostic awareness and to perform a barium follow-through examination in patients with undiagnosed gastrointestinal symptoms.

Surgery for primary neoplasia of the small intestine

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In a retrospective analysis, 25 patients with malignant small bowel tumour were studied. There were nine patients with carcinoid tumour, seven with leiomyosarcoma, seven with adenocarcinoma, one with malignant schwannoma and one with lymphoma. Definitive diagnoses were made by ultrasonography and contrast study of the gastrointestinal tract. Nevertheless, months or even years elapsed before diagnosis was established. In only 14 patients could curative resection be accomplished. In the remaining patients, hepatic metastases were found or the tumour could not be resected further because of its size. In six patients, adjuvant regional intra-arterial chemotherapy of the liver was carried out. The mean survival time for the whole patient group was 19 months. Patients who had undergone complete resection of the tumour had a significantly longer survival time (mean 25 months) than patients who had undergone a palliative operative procedure (mean 14 months). The mean survival time for patients with leiomyosarcoma was 38 months, adenocarcinoma 14 months and carcinoid tumours 22 months. Because of difficulties in establishing the diagnosis, a tumour of the small intestine should be considered in any patient complaining of abdominal pain.

Effect of somatostatin on experimental intestinal obstruction and tumour necrosis factor

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Intestinal obstruction is a very common surgical problem with a high morbidity and mortality. Recently, clinical improvement and histological changes of intestinal mucosa have been reported with intravenous

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perfusion of somatostatin-14. The objective of this work is to establish whether histological changes obtained with somatostatin are correlated with changes in the intraluminal production of tumour necrosis factor (TNF).

Thirty Wistar rats of mean(s.d.) weight 340(15) g were used. In each, a 10-cm closed-loop obstruction was created with ligatures in the ileum for 24 h. Half of the animals were infused with intravenous physiological serum ($0{\cdot}1\ \mathrm{ml\,h^{-1}}$) for 24 h (PS), the other group with somatostatin $2\ \mathrm{ng\,h^{-1}}$ and every rat was killed for histological study (presence or absence of inflammatory infiltrate, haemorrhage and mucosal necrosis), and measurement of TNF in intraluminal liquid between ligatures (mouse TNF ELISA kit). The histological results were expressed with a score (0, normal; 3, maximal) and TNF values as mean(s.d.) and were analysed with a statistical test.

The microscopic pathological scores from closed-loop segments in PS rats were 2·6(0·2) *versus* 0·4(0·2) in somatostatin rats ($P<0{\cdot}05$). The values of TNF were 407·2(49·98) in PS *versus* 147·4(50·31) in somatostatin rats ($P<0{\cdot}001$). In this model, somatostatin gives less histological intestinal damage and decreases TNF values inside the intestinal loop.

Foreign material in postoperative adhesions in man

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Postoperative adhesion formation is potentiated by the introduction of foreign materials, as is proved by animal experiments. Such adhesions often contain foreign body granulomas. Since little is known about this in humans, a study of 119 patients scheduled for relaparotomy was performed. The presence, distribution and quality of adhesions was scored during the operative period, and adhesion samples were taken for microscopic examination.

Adhesions were present in 94 per cent of the patients. Most frequently these were attached to small bowel (89 per cent) and omentum (83 per cent), followed by abdominal wall (66 per cent), colon (55 per cent), liver (53 per cent), stomach (33 per cent), female reproductive organs (19 per cent), retroperitoneum (15 per cent) and spleen (14 per cent). Significantly fewer adhesions were found in patients with a history of only one minor operation, compared with those with one major or multiple laparotomies ($P<0{\cdot}05$). Foreign body granulomas were found in 22 per cent of patients. These were caused by suture (16 per cent), starch glove powder (3 per cent) or a combination of the two (3 per cent). When granulomas were present, the median interval between the present and most recent laparotomy was 4 months. When granulomas were absent, this interval was significantly longer ($P = 0{\cdot}001$, Mann–Whitney test), namely 36 months. In other words, foreign body granulomas were more often found in patients recently operated on. For instance, in patients operated on no longer than 6 months before, granulomas were present in 71 per cent. In patients who had had a laparotomy performed more than 6 months before, granulomas were present in 13 per cent.

In conclusion, following laparotomy adhesion formation nearly always occurs. In recent adhesions foreign body granulomas occur in large percentages. This strongly suggests that the intra-abdominal presence of foreign material is an important cause of adhesion formation. Intra-abdominal contamination with suture and glove powder should therefore be avoided.

Prognostic factors in villous tumours of the duodenum

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A multicentre, retrospective study to evaluate the prognostic factors influencing survival of patients with villous tumours of the duodenum was carried out by the French Surgical Associations from November 1974 to January 1991. There were 20 women and 18 men (mean(s.d.) age 60(11·5) (range 38–81) years). Associated diseases were cancer of the gastrointestinal tract ($n = 4$), duodenal ulcer ($n = 3$), polyposis coli ($n = 1$) and Gardner's syndrome ($n = 1$). Symptoms were epigastric pain ($n = 17$), jaundice ($n = 12$), vomiting ($n = 9$), diarrhoea ($n = 8$), acute gastrointestinal haemorrhage ($n = 3$) and ten patients were symptom-free. Cholestasis was diagnosed in 13 patients and anaemia in four.

Gastrointestinal barium series ($n = 32$) had a sensitivity of 84 per cent and endoscopy ($n = 35$) a sensitivity of 100 per cent for the diagnosis of villous tumours. The location of the villous tumours was in the first part of the duodenum in two patients, the second part in 31, third part in three and fourth part in one. Survival curves were established according to Kaplan–Meier and compared with the log rank test. The median follow-up was 75 months.

Treatment involved limited resection of the duodenal wall ($n = 15$), a pancreatoduodenectomy ($n = 12$), limited resection with reconstruction of the biliary and pancreatic ducts ($n = 6$) and a palliative procedure in five patients. The histological data were: villous ($n = 18$), tubulovillous ($n = 7$) and villous tumours with a malignant component ($n = 10$). The sensitivity and specificity of preoperative biopsy to detect a malignant component in villous tumours was 50 per cent.

Overall survival rate was 81·2 per cent at 2 years and 47·4 per cent at 5 years. Survival and recurrence rates were not affected by the existence of a malignant component to' the villous tumours. Limited resection and reconstruction of the biliary and pancreatic ducts was associated with a statistically higher recurrence and mortality rate, compared with the two other curative treatments ($P < 0{\cdot}05$).

This series shows that limited resection of villous tumours located near the papilla of Vater carries a high risk of recurrence. It seems necessary to perform pancreatoduodenectomy.

Statistics concerning 80 cases of Meckel's diverticulum

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Eighty patients with Meckel's diverticulum seen over a 40-year period are reported.

In this series, the incidence of finding Meckel's diverticulum was 2 per cent of the total number of patients undergoing laparotomy, the highest incidence being in patients who were less than 20 years of age (48 cases) or more than 50 years old (13 cases).

Clinical diagnosis is rather difficult. Meckel's diverticulum may produce haemorrhage, inflammation, and obstruction in children and young adults. Alternatively, it may present as obstruction of the small intestine in a patient with fever but who had had a previous appendicectomy. In the present series Meckel's diverticulum caused inflammation in 38 patients, obstruction in 23, and haemorrhage in three.

The surgical treatment was removal of Meckel's diverticulum by local excision in 55 patients or by segmental resection of the small intestine in 34; two deaths occurred.

Effects of the somatostatin analogue octreotide in experimental small bowel obstruction

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Two groups of 20 Wistar rats were subjected to total obstruction of the jejunum. Octreotide administration $0{\cdot}35\ \mu\mathrm{g\,kg^{-1}}$ twice daily was instituted in the first group and saline in the second (control) group. Some 2 days later, all rats underwent operation for measurement of diameter of the bowel, determination of luminal loss of sodium and potassium, and for resection and anastomosis of the obstruction. At intervals, the animals were killed and bursting pressures, tissue hydroxyproline levels and histopathological evaluation of the anastomoses carried out. Distension of the ligated bowel was found to be significantly lower in the first group (0·74 *versus* 1·05 mm; $P < 0{\cdot}05$). The luminal losses of sodium and potassium were 0·03 *versus* $0{\cdot}06\ \mathrm{mmol\,ml^{-1}}$ and 0·0016 *versus* $0{\cdot}0024\ \mathrm{mmol\,ml^{-1}}$ ($P < 0{\cdot}01$). Anastomotic bursting pressures were significantly higher in the first group on the seventh day ($P < 0{\cdot}05$). Tissue hydroxyproline concentration showed no significant difference, but ischaemic changes were significantly less in the first group ($P < 0{\cdot}05$). It has been concluded that octreotide administration after small bowel obstruction enhances the distension of bowel, the loss of intraluminal water, sodium and potassium, and ischaemic changes in the bowel wall.

Endocrine

Subtotal thyroidectomy in euthyroid and hyperthyroid goitre

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A series of 268 patients operated on for euthyroid and hyperthyroid goitre over 10 years is reported. In the first 7 years unilateral subtotal lobectomy (USL) was performed if the contralateral lobe was normal and bilateral subtotal thyroidectomy (BST) if the goitre was bilateral; in the last 3 years BST was performed electively in every case. Patients were discharged without hormone replacement, thyroid function was assessed at 2 months and thyroid hormone was given only in cases of subclinical or clinical hypothyroidism.

The recurrence rate (three of 135; 2·2 per cent) and complication rate (four of 135; 3·0 per cent) were low; thus, total thyroidectomy for benign goitre is not warranted. As recurrence rates are higher after USL than after BST (two of 36 *versus* one of 99), and USL reduces but does not abolish subclinical hypothyroidism (seven of 36), BST is now considered to be the method of choice.

Surgery for secondary hyperparathyroidism

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A series of 231 patients with hyperparathyroidism is reported. In all, 78 cases of primary hyperparathyroidism, 137 cases of secondary hyperparathyroidism with chronic renal failure and 16 cases of tertiary hyperparathyroidism were treated between 1975 and 1992. In secondary hyperparathyroidism two forms of therapy were prevalent: subtotal parathyroidectomy and total parathyroidectomy with autotransplantation.

Subtotal parathyroidectomy, which was performed in 35 cases (25·5 per cent), must leave adequate vascularization of the residual hemiparathyroid. Total parathyroidectomy was performed in 102 cases (74·5 per cent). A parathyroid implant into a muscular pouch of the forearm is required. The implant consists of thin slices of parathyroid that have been sectioned under the microscope so that they are more adequately nourished and, therefore, more functional. The results obtained, compared with the literature, show that there are no radical differences between these two methods: recurrence of hyperparathyroidism is 7·4 per cent for subtotal parathyroidectomy and 4 per cent for total parathyroidectomy with autotransplantation; persistent hypoparathyroidism is present in 3·7 per cent *versus* 4 per cent.

The authors concluded that subtotal or total parathyroidectomy with autotransplantation are both good methods if correctly performed; total parathyroidectomy with autotransplantation has been performed more frequently because it permits an easier follow-up of patients and, in cases of recurrent hyperparathyroidism, an easier resection of the hyperplastic parathyroid of the forearm.

Primary hyperparathyroidism: experience with 59 patients undergoing operation

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Fifty-nine patients (44 women, 15 men) underwent surgery for primary hyperparathyroidism (pHPT) at the authors' institution between 1981 and 1991. The main diagnostic indications were nephrolithiasis in 59 per cent and skeletal complaints in 12 per cent. The most common complaints of the patients were related to the gastrointestinal tract (46 per cent) and the skeleton (39 per cent). Three patients had no symptoms.

The most useful diagnostic procedures were ultrasonography and computed tomography with a sensitivity of 40 and 20 per cent respectively. Histological examination of the parathyroid gland tissue showed adenoma in 68 per cent, hyperplasia in 29 per cent and carcinoma in 4 per cent. Forty-three patients were followed at a mean of 58·8 months. The success rate of the primary operation was 70 per cent. Persistence and recurrence of pHPT was observed in 16 and 12 per cent respectively. A high recurrence rate of 75 per cent was seen in patients with MEN I syndrome (four cases). The success rate in patients with adenoma (79 per cent) was higher than that in patients with hyperplasia (50 per cent). The two patients with carcinoma both showed normal calcium levels after 17 and 125 months. Permanent hypoparathyroidism was observed in only one patient.

Subtotal thyroidectomy for Graves' disease: a review of 100 cases

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The use of radioiodine for definitive treatment of Graves' disease has been increasing. However, there is a high incidence of hypothyroidism which requires a long-term follow-up, even in euthyroid patients. Surgery also has a high incidence of hypothyroidism, but this usually occurs early after thyroidectomy. Experience has been reviewed in the surgical treatment of 100 patients diagnosed with Graves' disease.

A group of 16 men and 84 women, mean(s.d.) age 31·9(11·8) years, diagnosed as having Graves' disease underwent subtotal thyroidectomy because of recurrence of hyperthyroidism after 1 year of antithyroid drug therapy or resistance to medical treatment. Patients were divided into three groups according to goitre size (1, only palpable; 2, visible; 3, very large). Surgical outcome was analysed to define a better-prognosis group. Statistical evaluation was with Student's *t* test.

Two patients (2 per cent) became hypoparathyroid, one of group 1 and one of group 2. They both require treatment with calcitriol. Five patients remained hyperthyroid after surgery and were treated with radioiodine (three of group 2 and two of group 3). They all thereafter became hypothyroid. Of the 95 successfully treated patients, 55 (58 per cent) became hypothyroid (thyroid-stimulating hormone level $> 5\ \text{mU ml}^{-1}$) at 12 months after surgery. The incidence of hypothyroidism is 73 per cent for group 1, 61 per cent for group 2 and 37 per cent for group 3.

When euthyroid and hypothyroid patients were compared, they showed significantly different mean(s.d.) goitre weights (60·9(28·7) g for hypothyroid and 81·5(44·7) g for euthyroid, P = 0·007).

Surgery is an effective treatment for hyperthyroid Graves' disease. A lower thyroid weight is associated with a higher incidence of postsurgical hypothyroidism. In patients with a larger goitre, subtotal thyroidectomy should be considered as a treatment of choice, as hypothyroidism is much less frequent.

Thyroid cancer: a study of 250 case reports

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Although thyroid cancer represents only 25 new cases per million population per year and has a mortality rate of 10–15 cases per million population per year, it is of clinical significance. A total of 250 case reports of patients with thyroid cancer were studied: patients were predominantly women (n = 215), with a mean (range) age of 44 (12–81) years. The tumour was located in the right lobe of the gland in 43 per cent of cases. Pathological distribution was papillary in 131, anaplastic in 13, follicular in 76, medullary in eight, and in Hürthle cells in 22 cases.

Total thyroidectomy was performed in 47 per cent of patients and hemithyroidectomy in 43 per cent. The morbidity and mortality rates were 12·4 and 4·5 per cent respectively.

Thyroid cancer was found to be more frequent in women, except when there was an intrathoracic location. Papillary cancer appeared in younger patients, while anaplastic pathology was more prevalent in older patients. Hyperthyroidism and multinodularity did not result in a lower risk of thyroid cancer. Of these patients, 78 per cent had a cold nodule on scintigraphy, but hot nodules were also seen. Metastasis was more frequent in the follicular type and recurrence was more frequent in patients with Hürthle cell tumours.

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Hürthle cell adenoma of the thyroid gland

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Hürthle cell neoplasms of the thyroid gland are uncommon but potentially lethal lesions whose treatment is controversial because of a lack of information about their biological and clinical behaviour. Based on histological criteria Hürthle cell tumours cannot always be accurately divided into benign and malignant. Unexpected late recurrences of an adenoma previously labelled as benign have been reported.

From a total of 502 primary thyroid epithelial tumours (1981–1991), after accurate analysis 35 (6·9 per cent) Hürthle cell adenomas were found. The selection of cases was made by evaluating multiple capsular blocks. Patients with lesions characterized by the coexistence of cellular atypia, frequent mitoses and invasive features (vascular, capsular or stromal) were excluded, as were those with only a Hürthle cell component in a papillary or follicular adenoma. Histology and electron microscopy were used to evaluate surgical specimens.

The following operations were performed: 29 hemithyroidectomies and six subtotal thyroidectomies. Based on the presence of multicentricity or coexisting carcinoma, five patients were reoperated on with complete excision of the remnant thyroid lobe. No operative death was recorded. The duration of follow-up after surgery ranged from 8 months to 9 years (mean(s.d.) 2·4(1·4) years). Two patients previously submitted to hemithyroidectomy developed a Hürthle cell carcinoma in the remnant lobe, after 3 and 6 years. In these two cases total excision of the thyroid gland was performed. In one of these, a radical neck dissection because of involved lymph nodes was necessary. After 3 years, the two patients are alive without distant recurrence.

The results suggest that total thyroidectomy is not always necessary and that electron microscopic criteria are useful to understand the nature and predict the biological behaviour of Hürthle cell adenomas.

Thyroperoxidase immunodetection in the diagnosis of malignancy of thyroid nodules using fine-needle aspiration

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The aim of this study was to investigate the value of thyroperoxidase (TPO) immunodetection in the diagnosis of malignancy of thyroid nodules using fine-needle aspiration (FNA). A total of 300 representative preoperative samples were examined. Slides were air-dried and stained with anti-TPO monoclonal antibody 47. According to the percentage of TPO-positive epithelial cells, patients were divided into two groups: benign (≥ 80 per cent) and malignant (< 80 per cent).

In 279 cases, additional slides were available for Giemsa stain and conventional cytology. Patients were divided into two groups: benign, and suspect or malignant. All patients underwent surgery and the final histological diagnosis was recorded as benign in 248 cases and malignant in 52 (44 papillary and eight follicular carcinomas).

	Cytology			TPO immunodetection		
	No.	Benign	Suspect/ malignant	No.	Benign	Malignant
Histology						
Benign ($n = 248$)	231	183	48	248	215	33
Malignant ($n = 52$)	48	4	44	52	0	52

The sensitivity of TPO immunodetection in the diagnosis of malignancy is 100 per cent and that of cytology 91·6 per cent; their specificity is 86·7 and 79·2 per cent respectively.

It is concluded that TPO immunodetection is a highly sensitive and specific method of detecting malignancy in FNA of thyroid nodules. It should become an essential adjunct in the preoperative cytological examination of such nodules.

Successful allotransplantation of microencapsulated parathyroids in rats

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The various roles of parathyroid hormone in metabolism make drug therapy for persistent hypoparathyroidism difficult. However, this does not justify parathyroid allograft with subsequent immunosuppression. Reduction of the immunogenicity of tissue using culture passages is rarely successful. Thus, the authors tried to protect the parathyroid transplants against an immunological response while maintaining the function of the glands using microencapsulation.

Parathyroidectomy was performed on 28 Lewis and 14 DA rats. After passage in tissue culture for 6 days, half of the parathyroid glands of the Lewis rats were microencapsulated, and 10:1 (donor:recipient) isotransplanted ($n = 7$) and allotransplanted ($n = 7$). The other half was treated similarly, except for the microencapsulation ($n = 7$ each). Serum calcium levels were tested on the day before parathyroidectomy and 7 and 14 days afterwards in the donors, and, additionally, every week in the recipients. A successful transplantation was defined as an increase of a serum calcium level from <1·6 mmol l^{-1} to >1·9 mmol l^{-1}. At 3 months after implantation, a histological examination was performed of the region of the transplant.

Before the study, all animals were normocalcaemic. After parathyroidectomy, all became hypocalcaemic with a mean serum calcium level of 1·55 mmol l^{-1}. Six weeks after transplantation all isotransplanted and one of seven allotransplanted rats without microencapsulation were normocalcaemic, and four of seven isotransplanted and zero of seven allotransplanted after 12 weeks. In the group with microencapsulated transplants, all seven isotransplanted and six of seven allotransplanted rats became normocalcaemic; after 4 months the numbers were four and five respectively. The histological examination of functionally successful transplantations revealed intact glands; if transplant was not successful there was only a fibrotic remnant of glands. There was no difference in pericapsular lymphocytic and fibroblastic infiltration between isotransplanted and allotransplanted animals.

In an animal experiment, microencapsulated parathyroid tissue both isografted and allografted can survive and function in a host. The microcapsule protects the transplant successfully from a foreign-body reaction by the recipient.

Salivary laser lithotripsy with spectroscopic feedback

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Endoscopic laser lithotripsy has provided a less traumatic alternative to electrohydraulic and electromagnetic lithotripsy in the treatment of urinary and biliary calculi. However, the small diameter of the ductal systems of salivary glands precludes the use of such endoscopic techniques in the treatment of sialolithiasis. An alternative method of directing the laser photon beam can be achieved by a technique known as spectroscopic feedback analysis. This technique was used on 13 salivary stones *in vitro*. It was also performed on two submandibular calculi in freshly excised submandibular glands. The glands and ducts were examined histologically for damage after treatment. The results indicated that the laser fragmented all the calculi treated *in vitro*. There was no evidence of damage to the duct or gland from the laser beam. This technique offers a non-invasive method of removing salivary calculi while retaining the function of the gland.

Cytokines in thyroid autoimmune infiltrate

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T lymphocytes are regulated by a complex network of soluble polypeptides called cytokines, which are involved in the development and perpetuation of autoimmune diseases. Thyroid autoimmune infiltrate shows an unusual pattern of cytokine production, but until now all studies have been performed *in vitro*. The aim of the present study was to assess cytokine production *in vivo*. Ten patients with Graves' disease and two with goitrous Hashimoto's thyroiditis underwent subtotal thyroidectomy. Three patients with toxic and eight with non-toxic nodular goitre were included as controls. Venous blood (5 ml) was drawn during surgery, either from one of the major epithyroidal veins or from a forearm vein. All blood samples were immediately centrifuged and frozen. The assayed cytokines, all by immunoenzymatic methods, included interleukin (IL) 1β, IL-2, IL-6, interferon γ and tumour necrosis factor α. Serum concentration was in the normal range for all cytokines, both in the thyroidal and peripheral venous blood, with no significant difference between the autoimmune and non-autoimmune patients. No cytokine showed a difference between thyroidal and peripheral blood. The failure to detect significant local cytokine production could be for several reasons: all patients with Graves' disease were receiving antithyroid drugs; locally produced cytokines could have a half-life so short that they disappeared before reaching the epithyroidal veins; only two patients with Hashimoto's thyroiditis, the condition expected to display the highest activation of the thyroid destructive autoimmune effector mechanisms, were included in the study. Interestingly, one of the two patients with Hashimoto's thyroiditis showed a clear positive gradient between thyroidal and peripheral blood for IL-2 and IL-6. IL-2 production is consistent with the presence of an active autoimmune infiltrate. From previous studies *in vitro*, it may be suggested that IL-6 production derives not only from infiltrating lymphocytes but also from direct thyrocyte secretion. This is believed to be the first study to assess cytokine production *in vivo*.

Diagnostic procedures for thyroid nodules

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Although the management of thyroid nodules is a common problem, it remains controversial. One of the reasons for this is uncertainty about the reliability of diagnostic procedures. A study to clarify the reliability of physical examination, ultrasonography (US) and fine-needle aspiration cytology (FNAC) for the diagnosis of thyroid nodules was therefore conducted.

A total of 252 patients with thyroid nodules who underwent thyroid surgery at Tokyo Women's Medical College during 1987–1991 were studied. The patients comprised 126 with benign lesions (adenoma or adenomatous goitre), 114 with papillary carcinoma and 12 with follicular carcinoma. Preoperative diagnoses (negative or positive for carcinoma) made by physical examination, US and FNAC were checked from the patients' medical records, and the sensitivity and specificity of each diagnostic procedure calculated.

The specificity of physical examination, US and FNAC was 98 per cent (123 of 126), 90 per cent (113 of 126) and 98 per cent (124 of 126) respectively. The sensitivity of physical examination, US and FNAC for all carcinomas was 63 per cent (80 of 126), 78 per cent (98 of 126) and 80 per cent (101 of 126), respectively. However, after taking account of the histological categories of carcinoma, the sensitivity of physical examination, US and FNAC was 68 per cent (77 of 114), 83 per cent (95 of 114), 88 per cent (100 of 114) for papillary carcinoma and 25 per cent (three of 12), 25 per cent (three of 12) and 8 per cent (one of 12) for follicular carcinoma respectively. When all the test results were negative, the likelihood ratio favouring papillary carcinoma was 0·008 whereas that of follicular carcinoma was 0·6.

The histological category of a carcinoma should be considered when evaluating the reliability of diagnostic procedures for thyroid nodules, as the overall sensitivity of the diagnostic information depends on the frequencies of the categories in the sample. These investigations are unable to exclude follicular carcinoma, either individually or in combination.

Review of 7 years' experience with fine-needle aspiration biopsy of the thyroid

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In the past 7 years, 1936 fine-needle aspiration biopsy (FNAB) procedures of the thyroid were performed on 1881 subjects with one or more thyroid cold nodules, either solitary or in the setting of an adenomatous goitre. Adequate material was obtained from 1862 FNAB procedures (96·2 per cent) and the diagnosis was negative for cancer in 88·5 per cent, suspicious in 8·4 per cent and positive for cancer in 3·1 per cent. Histological evidence after surgery in 311 cases (16·7 per cent) showed malignancy in 3·2 per cent of the 'negative' cases, in 21·1 per cent of 'suspicious' and in 93·8 per cent of patients positive for cancer on FNAB. A cytological diagnosis negative for cancer was usually followed by clinical observation, and only 187 patients had resection. A malignant tumour was found after surgery in six patients. Surgery was always recommended after suspicious FNAB and a malignant tumour was found in 16 of 76 cases. A positive diagnosis was an absolute indication for prompt surgery. Histological confirmation was obtained in 48 patients, five patients had an inoperable tumour and four refused. Analysis showed a false-negative rate of 2·6 per cent, false-positive rate of 1·3 per cent, sensitivity of 88 per cent, specificity of 98 per cent, positive predictive value of 94 per cent, negative predictive value of 97 per cent and accuracy of 96 per cent. Addition of the suspicious cases to the positive increases the sensitivity to 91 per cent.

These findings offer further evidence of the reliability of FNAB in the evaluation of thyroid nodules, especially when the procedure is performed by skilful operators and close cooperation established between clinician and pathologist.

Zollinger–Ellison syndrome: surgical treatment for 'cure' or long-term palliation

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Since 1970, 51 patients with Zollinger–Ellison syndrome have been observed; 11 had a MEN type I with two or more endocrine glands involved; 24 had a portal venous sampling (PVS) before surgery for tumour localization and evaluation of resectability.

Twenty-eight patients underwent surgery; 11 had only a total gastrectomy because the tumour was not found. Seventeen patients underwent resection, 13 having a PVS performed before surgery that in eight showed only a single source of gastrin. All eight cases became normogastrinaemic after operation (follow-up 5–16 years). Only one of the five patients in which PVS did not localize a single tumour was cured by surgery. Only one of the four patients who underwent surgery without prior PVS was made normogastrinaemic by resection. Thus gastrin fell to normal in ten of 28 patients surgically treated, but in two patients a late recurrence of hypergastrinaemia was found after 5 and 14 years. Patients in whom gastrin did not fall to normal were treated with antisecretory drugs. Of the 26 patients who had medical treatment three needed later emergency surgery (between 3 months and 3 years) while nine required omeprazole for long-term failure of H_2 blockers (3–14 years). Five patients had liver metastases at the time of diagnosis; two died within 12 months. Two patients (one total gastrectomy, one medical treatment) developed liver metastases 21 and 15 years later respectively.

PVS greatly enhances the chance of tumour resection. Careful and lifelong follow-up is mandatory for all patients. Patients having long-term medical treatment should undergo periodic re-evaluation for possible resectional surgery.

Surgical treatment of insulinoma

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The role of preoperative and intraoperative procedures for localization of insulinoma has been extensively debated in recent years. Transhepatic portal sampling (THPS) before surgery has been recommended when other tests fail to localize the tumour.

To determine the role of different investigations, 52 patients with insulinoma operated on in three consecutive periods are reviewed. Fifteen patients investigated by arteriography had successful resection in 13 cases. One was found at a second exploration and one has been found after second exploration using intraoperative ultrasonography. Twenty-six patients had exploration after THPS; the tumour was found in all 25 patients operated on in this hospital. Twelve procedures performed using intraoperative ultrasonography without THPS were successful, although three intraoperative localizations failed. Left-sided resections successfully cured symptoms in two of these.

High success rates for surgical treatment of insulinoma can be achieved with THPS or intraoperative ultrasonography. THPS is therefore unnecessary before a first operation on the pancreas for insulinoma.

Endocrine metabolic and blood pressure disturbances in the morbidly obese: modifications after Mason's vertical banded gastroplasty

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An analysis of the development of endocrine and metabolic changes was undertaken in a series of patients with morbid obesity who underwent a Mason's vertical banded gastroplasty.

Between November 1986 and April 1992, 50 patients who suffered from morbid obesity were subjected to a Mason's vertical banded gastroplasty. The following clinical and analytical parameters were studied after operation: glucose, cholesterol, triglycerides, sex hormones and blood pressure. The changes were observed after 6 months, which coincided with a period of fast weight loss, and again 1 year after surgery, during a period of weight stability. The outcome was then compared with preoperative findings.

A progressive decrease in glucose and triglycerides levels in the blood was seen, with a significant statistical difference ($P < 0{\cdot}05$). Cholesterol levels did not change. Systolic and diastolic blood pressure values also decreased to normal values in most patients, with statistical significance. The amounts of oestradiol, progesterone, androsterone and cortisol in the blood were disturbed in two cases (4 per cent), and high levels of aldosterone were found in ten (20 per cent) patients. Urinary testing of sex hormones and their fragments showed a high rate of anomalies, with a decrease of the values of 17-OH corticoids, 17-ketosteroids, dihydroepiandrostenedione, and aetiocholanolone.

A progressive decrease of glucose and triglyceride levels in the blood was obtained in this study. Systolic and diastolic blood pressure values also decreased to normal values. Disturbances were resolved in 80 per cent of patients once they achieved weight stability.

Clinical, histological and immunohistochemical study of phaeochromocytoma: analysis of 30 patients

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A total of 34 consecutive cases of phaeochromocytoma occurring between 1981 and 1989 were identified from the Royal Postgraduate Medical School pathology index. Full pathological, clinical and follow-up data were available on 30 cases. Some 18 patients were male and 12 female (M:F 3:2); age at presentation ranged from 18 to 59 (median 43) years. Eighteen cases involved only the right adrenal gland, 11 cases involved only the left adrenal and one case was bilateral (associated with MEN IIA).

Sections were cut from paraffin blocks for morphological and immunohistochemical analysis. The following immunohistochemical markers were employed: cytokeratin, vimentin, desmin, S-100 protein, epithelial membrane antigen, neurone-specific enolase, chromogranin, neuropeptide tyrosine (NPY), C flanking peptide of NPY, Met-encephalin, dopamine-B-hydroxylase, proliferating cell nuclear antigen (PCNA) and p53 protein.

Of the 30 cases studied, only two manifested malignant behaviour, in each case liver metastasis. Morphologically, one of these cases exhibited the characteristic small cell pattern. Neither of the malignant cases was associated with MEN IIA or IIB syndromes, von Hippel–Lindau disease or neurofibromatosis. There was no clear difference in immunohistochemical staining between the benign and malignant tumours. Nuclear p53 expression was weak or absent in all cases, and no correlation was seen between PCNA reactivity and prognosis.

Ultrasonographically guided fine-needle aspiration cytology in the early diagnosis of carcinoma in multinodular goitre

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The incidence of unsuspected malignancy in multinodular goitre (MG) confirmed by histology is 3·7 per cent in this institution. Some 76 malignancies were found in 2052 surgical specimens of patients operated on for MG in the period 1976–1991. The value of ultrasonographically guided fine-needle aspiration cytology (FNAC) was estimated in a group of 100 consecutive patients undergoing surgery for clinically benign MG in 1992. Surgical indications included cosmesis, compressive symptoms and hyperthyroidism. Each patient had at least two punctures for FNAC; a 22-G ultrasonographically guided needle was inserted into the visualized lesion and aspirated. All samples were evaluated by a single cytopathologist. Patients with suspected malignancy according to FNAC had frozen section at the time of the planned procedure and the decision about the extent of thyroid resection was then made. Otherwise, standard subtotal thyroidectomy was performed. The results of FNAC were compared with histological diagnosis from resected specimens made by an independent pathologist. There were eight true-positive FNAC reports, 89 true-negative, one false-positive and two false-negative. Therefore the sensitivity of FNAC in the diagnosis of carcinoma in MG was 80 per cent, specificity 98 per cent, positive predictive value 88 per cent and accuracy 97 per cent.

Surgical therapy and prognostic factors in medullary thyroid carcinoma: evaluation of the German MTC study

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A total of 741 patients were reported in the German medullary thyroid carcinoma (MTC) register up to 1991. In the initial operation, total thyroidectomy was performed in 82 per cent of patients and dissection of lymph nodes in 48 per cent; in cases in which the diagnosis was known before surgery, these rates increased to 88 and 76 per cent, respectively. The 10-year survival rate for familial forms was 72 per cent and for sporadic forms 62 per cent. In a univariate analysis, the stage of disease at diagnosis, age, sex and type of disease were significant prognostic factors, with a better prognosis for young female patients with familial disease at an early stage. In a multivariate analysis, the difference in the survival rates of patients with familial disease *versus* those with the sporadic form disappeared, while prognostic information provided by age and sex was still significant. There seems to be no difference in biological behaviour between tumours of the sporadic and those of the familial type.

Gastric cancer

Evaluation of CA 72.4 in patients with gastric cancer

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The CA 72.4 assay measures the tumour-associated glycoprotein TAG 72 using two monoclonal antibodies, B72.3 and CC49. The aim of this work was to evaluate the clinical usefulness of this marker in patients with gastric cancer. Also CA 72.4 was compared with carcinoembryonic antigen (CEA) and CA 19.9.

Serum levels of CA 72.4, CEA and CA 19.9 were determined in 70 healthy volunteers and before operation in 70 patients with gastric adenocarcinoma. The groups were homogeneous for age and sex. All patients with gastric cancer were staged according to the tumour node metastasis classification as IA ($n = 4$), IB ($n = 4$), II ($n = 8$), IIIA ($n = 8$), IIIB ($n = 9$) or IV ($n = 37$). At a specificity of 95 per cent the sensitivities for identification of disease of CEA, CA 19.9 and CA 72.4 were 0·26, 0·27 and 0·54 respectively and the cut-off levels 6 ng ml^{-1} for CEA, 51 µg ml^{-1} for CA 19.9 and 4·6 µg ml^{-1} for CA 72.4. At 95 per cent specificity the combined use of CEA and CA 19.9, and CEA and CA 72.4, did not improve sensitivity (0·47 and 0·54 respectively), but the combination of CA 19.9 and CA 72.4 did improve sensitivity (0·60). The use of three markers increased the sensitivity to 0·64.

These results support the role of CA 72.4 as a reliable tumour marker in the study of patients with gastric cancer, because of its specificity and sensitivity.

Prognostic factors in early gastric cancer

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From 1979 to 1988, 332 patients with early gastric cancer (EGC) were operated on in 23 centres. There were 208 men and 124 women. Data were collected retrospectively and screened for prognostic effect. Eight local excisions (2·4 per cent), 235 partial (70·8 per cent) and 89 total (26·8 per cent) gastric resections were performed. Postoperative mortality rate was respectively 0, five (2 per cent) and nine (10 per cent) in the three groups. Total gastric resections were performed when EGC was located in the lower third of the stomach in 42 cases. Cumulative 5- and 7-year survival rates were 92 and 88 per cent. Mean follow-up was 56 months. During the follow-up period there were 23 related and 37 unrelated deaths. Five patients are alive with recurrence or metastases. Cause of death was unknown in two cases. In univariate analysis, the 7-year survival rate varied with lymph node involvement (91 per cent for 299 node-negative *versus* 60 per cent for 33 node-positive; $P < 10^{-4}$), depth of parietal spread (93 per cent for 159 mucosal *versus* 89 per cent for 167 submucosal lesions; $P = 0·05$), and tumour location (95 per cent for 212 in the lower third *versus* 86 per cent for 120 in the proximal stomach; $P = 0·05$). Modified Borrmann classification, histological type, size of the tumour, extent of resection or sex had no influence on survival rate. In multivariate analysis, three variables were associated with better prognosis: no lymph node metastasis ($P < 10^{-4}$), tumour of the lower third of the stomach ($P < 0·004$), and tumour size < 15 mm ($P = 0·02$).

Extent of lymph node dissection for carcinoma of the cardia

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Systematic lymph node dissection has been adopted as part of a standard procedure in patients undergoing curative resection for carcinoma of the cardia. Two series of patients have been compared: group A patients ($n = 132$) underwent proximal gastric resection with standard lymphadenectomy (R_1) and oesophagogastric anastomosis from 1970 to 1985. Group B patients ($n = 280$) underwent total or extended total gastrectomy with systematic lymphadenectomy (R_{2-3}) and Roux-en-Y oesophagojejunostomy from 1982 to 1992. Both patient groups were matched for age, sex, tumour node metastasis staging and histopathological type of tumour.

In group B, 148 patients were prospectively analysed. R_2 total gastrectomy was performed including *en bloc* excision of the whole stomach together with the distal 5 cm of the oesophagus, entire greater omentum, bursectomy and lymphadenectomy along the common hepatic and hepatic arteries, coeliac trunk and splenic artery, splenectomy, suprapyloric and infrapyloric lymph node dissection. The left gastric artery was always ligated at its origin. Distal pancreatic resection and splenectomy were performed in 27·7 per cent of patients; positive lymph nodes were found in 71·6 per cent of cases. Complete dissection of groups A and B (R_2) was achieved in 39·9 per cent; R_3 dissection was performed in 60·1 per cent. Absolutely curative resection was performed in 37·8 per cent, relatively curative resection in 44·6 per cent and non-curative resection in 17·6 per cent. Despite extensive lymphadenectomy, the postoperative mortality rate has steadily decreased: 25·9 per cent after proximal gastrectomy *versus* 5·4 per cent after total gastrectomy and systematic lymphadenectomy. Hence, extensive lymphadenectomy could be successfully performed without increasing mortality rates. The 5-year survival rate was 7·5 per cent in group B, compared with 39·8 per cent in group A.

Recurrence in early gastric cancer

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In a retrospective multicentre study of 172 cases of early gastric cancer (EGC), 11 patients died from recurrence of the gastric cancer and 13 died from unrelated causes. One patient with a gastric remnant recurrence was alive 3 years after the initial operation at the time of follow-up. The mean(s.e.) cumulative recurrence mortality rates were 7·5(2·1) per cent at 5 years and 9·4(2·7) per cent at 10 years (Kaplan–Meier method). The cumulative 10-year survival rate was 91·6(2·4) per cent excluding operative death and that from causes other than gastric cancer.

The recurrence patterns of EGC were blood-borne metastases to the liver (in four cases), recurrence from lymph nodes and peritoneum (in four cases), and recurrence in the residual stomach (five patients including those alive).

Univariate analysis showed a significant difference in recurrence mortality rates between cancers confined to the mucosa and those with submucosal invasion ($P = 0·044$) and between cancers of non-intestinal histological type and cancers of intestinal histological type ($P = 0·023$).

Using Cox multivariate analysis for eight variables (sex, age, depth of invasion, lymph node metastases, presence of ulceration, location, histological type, type of surgery), at the end of stepwise procedure adjusted for depth of invasion, age and histological type had the most significant effect on recurrence. The relative importance of the two factors was clarified by the risk ratios (5·25 for age and 4·41 for histological type).

The results of this analysis of factors influencing recurrence after surgical treatment of EGC showed a significant dominance of host- and tumour-related factors (age and histological type) over the type of surgical procedure performed.

Gastric cancer: long-term survival of patients with positive N_3 lymph nodes

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The aim of the study was to evaluate long-term survival of patients affected by gastric cancer with positive N_3 lymph nodes undergoing gastrectomy plus extended locoregional lymphadenectomy.

During the period 1981–1992, 184 consecutive patients with histologically proven adenocarcinoma of the stomach underwent resective surgery (total gastrectomy plus R_3 lymphadenectomy, 106; distal subtotal

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gastrectomy plus R_2 lymphadenectomy extended to hepatic pedicle and retropancreatic nodes, 78) at this surgical unit. According to Japanese nomenclature gastric resection was 'absolutely curative' in 135 N_{0-2} patients (N_{0-2} group) and 'relatively curative' in 15 N_3 patients (N_3 group). The 5-year survival rate (operative mortality excluded) was calculated according to the actuarial life-table method.

Overall 4·8 per cent (seven of 145) patients were lost to follow-up, 4·6 per cent (six of 131) in the N_{0-2} group and 7 per cent (one of 14) in the N_3 group. The 5-year survival rate was 62 per cent in the N_{0-2} group (83·0 per cent, 61·9 per cent and 45·6 per cent in stage I, II and III respectively) and 24·2 per cent in the N_3 group (stage IV). Among these, three N_3 patients are still alive 115, 79 and 44 months after operation. One additional N_3 patient died 63 months after operation without evidence of recurrent disease.

According to the unified tumour nodes metastasis staging system, N_3 positive lymph nodes in gastric cancer are regarded as M_1 (stage IV), therefore their expected 5-year survival should be zero. However, results of the present study show that, after R_3 gastrectomy, even N_3 patients can survive more than 5 years, thus confirming that the gastric resection should be considered, as in the Japanese nomenclature, 'relatively curative' rather than palliative. The therapeutic efficacy of extended lymphadenectomy in the surgical treatment of gastric cancer is confirmed.

Early gastric carcinoma: 8 years' experience

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The detection and diagnosis of early gastric adenocarcinoma is of great importance, as the outcome differs from that of advanced cancer and the 5-year survival rate is better. A total of 129 patients with gastric cancer were treated surgically during the past 8 years. The methods of investigation of the upper gastrointestinal tract were double-contrast barium meal and fibreoptic endoscopy, with at least six biopsies being taken from suspicious lesions.

Early gastric cancer was diagnosed in 13 patients (10 per cent; three women and ten men aged from 34 to 62 years). Chronic gastritis dysplasia was present in eight patients and intestinal metaplasia in five. Dysplasia and gastric polyps were observed in one patient who had been followed by endoscopy and biopsy at 6-month intervals for 2 years. Partial gastrectomy with Billroth II anastomosis was performed in eight patients. Five patients had total gastrectomy with reconstruction by Henley jejunal interposition. Lymph node metastases were detected in two patients who died at 24 and 32 months after the operation. The remaining patients are still alive without recurrence.

Endoscopic surveillance in patients presenting with dysplasia, or particularly with intestinal metaplasia, leads to early detection of gastric cancer and hence to better survival.

Gastric surgery

Influence of preoperative weight loss on effect of vertical banded gastroplasty

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Surgery is the only therapeutic method that has shown lasting results in the treatment of morbid obesity. Ability to lose weight by voluntary dieting has been associated with unsatisfactory weight loss after gastroplasty. This report examines the effect of preoperative intermaxillary fixation (IMF) on weight reduction induced by vertical banded gastroplasty (VBG).

A total of 24 patients entered the study and were randomly assigned to either 10 weeks of IMF or 10 weeks on the waiting list. Patient groups were similar with respect to age, sex and body mass index (BMI). All patients were urged to lose weight before operation. At the end of 10 weeks, all patients were operated on with a standard VBG (14–16 ml, 50-mm Marlex band).

Patients in the IMF group lost a median of 18 (range –12 to –36) kg, and the waiting list group lost 3 (3 to –30) kg during the 10 weeks before surgery. Total weight loss from time of inclusion to 24 months after operation was the same in both groups. Operating time, blood loss and postoperative hospital stay did not differ between the groups. There was no mortality.

	BMI (kg m^{-2})				Operation time (min)*
	Incl.	At op.	12 months	24 months	
IMF plus VBG	42·6	37·9	28·4	27·7	64 (57–90)
VBG	42·0	41·5	28·9	28·1	66 (53–86)

*Values are median (range)

These results suggest that weight loss up to 2 years after VBG is not influenced by preoperative weight loss as induced by IMF. Although no obvious advantage in having patients pretreated with IMF was found, the results indicate that jaw wiring can be used before operation for patients at risk of respiratory and other complications without endangering the 2-year result.

Clinical experience with biofragmentable Valtrac ring for sutureless anastomoses in Billroth I and II partial gastric resection

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The biofragmentable Valtrac ring (BVR) was used to create a functional and accurately sized gastroduodenostomy in Billroth I patients and a gastrojejunostomy in Billroth II patients with Brown's anastomoses. Twenty patients underwent partial gastric resection for complicated peptic ulcer disease: 13 patients had gastroduodenostomy (Billroth I) and seven patients gastrojejunostomy with Brown's anastomoses (Billroth II) using the BVR for sutureless anastomoses. In Billroth I patients the distal resection line was identified 1 cm below the pylorus and the proximal line was set exactly at the point of Mikulicz. At the distal resection line a purse-string clamp was adjusted, the duodenum was dilated up to 28 Ch and the BVR inserted. At the greater curvature and the TA90 stapler row a diameter of 28 Ch was created in the same fashion, the two parts narrowed and the gastroduodenostomy closed with a click. In Billroth II patients undergoing partial gastric resection the stomach was prepared in the same fashion as for Billroth I and the duodenal stump closed either with a GIA stapler or by hand. Thereafter the anastomoses were finished by inserting the BVR in the same way as described above for creating the gastrojejunostomy and the Brown anastomoses.

One postoperative complication occurred. This patient developed temporary mechanical small bowel obstruction because of delayed passage of ring fragments but did not need surgery. The Gastrografin test on the fifth day after operation showed no leakage of the anastomoses. A swelling could not be identified. The disappearance of the BVR was monitored by radiography. Only one emptying disturbance has been seen.

A tension-free gastroduodenostomy is an absolute requirement for a complication-free Billroth I resection. This is possible only if adequate mobilization of the duodenum has been performed and the duodenal wall is free of damage. The use of the BVR has therefore to be proved in every single case. As insertion of the BVR needs 1·5–2 cm of tissue, the duodenal stump has to be dissected free for at least 4 cm, otherwise the BVR is contraindicated. In Billroth II resections there are almost no contraindications for the use of the Valtrac ring. With exact indications the BVR offers a secure adaptation of the anastomotic wall layers and a more functional and anatomically accurately sized gastroduodenostomy and gastrojejunostomy with Brown's anastomosis.

Enterostomy: more and more a case of surgical endoscopy

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Since the introduction of percutaneous endoscopic gastrostomy (PEG) the performance of gastrostomy via a laparotomy has become rare. The simple and minimally invasive method of PEG is a great advantage for the severely ill patient with this indication. With the development of endoscopic techniques and growing experience PEG has become a very safe method, and more difficult procedures such as percutaneous endoscopic jejunostomy (PEJ) are now possible. If endoscopic passage into the stomach is impossible because of subtotal or total stenosis of the hypopharynx, oesophagus or cardia, percutaneous sonographic gastrostomy is an alternative. However, because of personal experience we prefer laparoscopic gastrostomy (LG) in these cases. The authors report on experience in indication, technical difficulties and complications after 96 PEG procedures, five PEJ and two LG, as well as on first results of percutaneous endoscopic caecostomy as a further possibility of endoscopic creation of an enterostomy.

Bariatric surgery for morbid obesity: transverse diverting or vertical banded gastroplasty: a comparative study with long-term follow-up

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A total of 79 bariatric procedures were performed over a period of 7 years: 23 were transverse diverting gastroplasty (TDG) operations (Alden or Griffen) and 56 vertical banded gastroplasty (VBG) (Mason). The mean age of patients in both series was 34 years; mean body-weight was 126 kg (mean 206 per cent of ideal weight, IW); there was no difference between groups in the change of the percentage of the IW which reached 120 per cent at 2 years' follow-up after successful treatment by either TDG or VBG. The failure rate of about 30 per cent at 2 years was similar in both series. The results (expressed in quartiles) as percentages of patients remaining overweight after treatment (excellent, 0–25 per cent; good, 26–50 per cent; fair, 51–75 per cent; poor, 76–100 per cent) show that 85 per cent of the TDG and 72 per cent of the VBG procedures gave excellent to good results, whereas 15 per cent of the TDG and 28 per cent of the VBG operations gave fair to poor results. A close follow-up of morbidly obese patients is mandatory.

In conclusion, the gastroplasties led to weight reduction in selected morbidly obese patients. Both TDG and VBG provide equal results in terms of long-term weight reduction or recurrence rate. Moreover, VBG is easier to perform, particularly in recurrent obesity.

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Vertical banded gastroplasty with Narbona's technique when treating morbid obesity in patients with gastro-oesophageal reflux caused by hiatal hernia

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The presence of hiatal hernia in obese patients may interfere with an antiobesity vertical gastroplasty. In this unit, a pexis of the round ligament is performed when treating gastro-oesophageal reflux, and a vertical banded gastroplasty is undertaken as an antireflux technique. Mason's technique and Narbona's technique are thus combined in morbidly obese patients with gastro-oesophageal reflux.

A total of 63 vertical banded gastroplasties were performed from November 1986 to November 1992. Four of these patients had concomitant hiatal hernia, for which they underwent vertical gastroplasty with Narbona's technique. These four patients comprised a 35-year-old man weighing 130 kg, a 29-year-old woman weighing 117 kg, a 22-year-old woman of 130 kg, and a 33-year-old man who weighed 120·5 kg. All four patients achieved weight loss without any evidence of gastro-oesophageal reflux (monitored by clinical, radiological or pH-metric techniques).

The combination of vertical banded gastroplasty with Narbona's technique is a useful method when treating morbid obesity associated with gastro-oesophageal reflux.

Roux-en-Y is a worthwhile procedure

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The Roux-en-Y procedure has varied in popularity. Recently, poor results have been reported for the procedure.

Two groups of patients are presented: group 1 in which the Roux operation was done to relieve the symptoms of alkaline reflux and group 2 in which the procedure was done at the time of initial gastric surgery with the aim of preventing biliary bile reflux. Group 1 consisted of 15 patients: 12 showed improvement in Visick grading, 40 per cent were asymptomatic on follow-up and 80 per cent felt that surgery had been worthwhile. One patient required further surgery for a duodenal stump leak and morbidity rates were low. Some 66 per cent of patients required no further medication. Group 2 consisted of 22 patients undergoing resection for gastric carcinoma. Of these 15 were in Visick grade 1 or 2; two were classified as Visick 4 but one has been converted to Visick 1 after further resection. The mortality rate was 14 per cent in this group and, in a 5-year follow-up, 50 per cent of the patients have died.

It is concluded that good or satisfactory results can be obtained from Roux-en-Y diversion for patients with benign (80 per cent satisfied) or malignant (83 per cent satisfied) lesions. There is no need to question conventional wisdom that the two anastomoses should be separated by at least 45 cm.

Stress and gastroduodenal disease in the young

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The importance of emotional stress in the pathogenesis of many gastrointestinal diseases is widely accepted, whereas its implications for the development of gastroduodenal disease in young people have not yet been thoroughly considered. In previous publications, the present authors noted that about 50 per cent of the young requiring emergency care had symptoms of gastrointestinal disease and that haemorrhagic gastroduodenitis and complicated peptic ulcer were (after trauma) the most common causes of urgent admission to hospital. Furthermore, a rise in the incidence of gastrointestinal pathology in young men during military service was observed and it was hypothesized that abrupt changes in lifestyle could generate an important adaptative stress, which facilitates the development of gastroduodenal disease.

A total of 385 symptomatic men ranging in age from 18 to 26 years underwent oesophagogastroduodenoscopy, of whom 60 were evaluated psychologically using the Minnesota Multiphasic Personality Inventory. This test provides information related to emotional state, coping ability and somatic conversion tendencies. From the clinical point of view, oesophagitis accounted for 29·2 per cent of all pathological findings and hiatus hernia for 15·5 per cent. Gastroduodenitis was present in 50·8 per cent of patients and peptic ulcer in 4·5 per cent. Preliminary psychological evaluation showed a generalized difficulty in reacting to stress, as indicated by high scores on the Depression and Psychoastenia scales. High scores were also obtained in the Hysteria scale when gastroduodenitis, in the erosive form, was present, thus indicating that anxiety and psychological discomfort tend to be turned into somatic symptoms. It was also noticed that gastrointestinal pathology arises most frequently during the first 5 months of military service, especially within the third and the fourth months. From military psychosocial studies, it is now known that this is the critical time for young people in the process of adaptation to a new lifestyle and, in this situation, stress stimulation is stronger.

Geriatric surgery

Non-elective colorectal surgery: effect of age on results

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Between 1986 and 1992, 150 consecutive patients underwent non-elective colorectal surgery. To determine whether age is the most important factor affecting outcome, patients were divided into two groups: group 1 included 65 patients aged <70 years, of mean(s.d.) age 55·5(12·5) years; group 2 comprised 85 patients aged ≥70 years, of mean(s.d.) age 79·1(5·4) years.

Colorectal resection was performed in 45 cases (69 per cent) from group 1 and in 42 (49 per cent) from group 2. Forty-two operations in group 1 (65 per cent) and 58 (68 per cent) in group 2 were performed for malignancy.

Other possible determining factors were also analysed: sex, the use of resective procedures, malignancy, reasons for surgery (peritonitis, bowel obstruction), number of risk factors (associated diseases), and admission–operation interval. As a result of multiple regression analysis it was found that local morbidity increased with age ($P < 0{\cdot}01$) and malignancy ($P < 0{\cdot}05$). Mortality rate (12 per cent in group 1 (eight of 65), and 32 per cent in group 2 (27 of 85)) was determined by the presence of associated risk factors ($P < 0{\cdot}001$), the presence of peritonitis ($P < 0{\cdot}05$) and by the admission–operation interval ($P < 0{\cdot}05$). It is concluded that age does not determine mortality in non-elective colorectal surgery even though it is a dominant factor in morbidity.

Age as a factor in decision-making for elective colorectal surgery

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This study analysed 440 consecutive colorectal operations performed between 1986 and 1992 in a retrospective review to find out whether age is a determinant factor in deciding whether or not to undertake elective colorectal surgery. The patients were divided into two groups: group 1 included 219 patients aged <70 years (mean(s.d.) age 56·5(11·8) years); group 2 comprised 221 patients aged ≥70 years (mean(s.d.) age 76·3(4·8) years).

Colorectal resection was performed in 175 cases (79·9 per cent) from group 1 and in 175 cases (79·2 per cent) from group 2. A total of 181 (82·7 per cent) operations in group 1 and 204 (92·3 per cent) in group 2 were performed for malignancy. Other possible determinant factors were also analysed: sex; whether colorectal resection was performed; number of risk factors (associated diseases); and tumour stage.

The results were analysed by multiple regression, and show that the morbidity rate (44·3 per cent in group 1 (97 of 219) and 56·1 per cent in group 2 (124 of 221)) increased with age ($P < 0{\cdot}01$), in men ($P < 0{\cdot}01$) and in patients who had undergone resection procedures ($P < 0{\cdot}001$). In cases in which resection was performed, male sex ($P < 0{\cdot}001$) and age ($P < 0{\cdot}05$) contributed to an increase in morbidity. Mortality rates (3·2 per cent in group 1 (seven of 219) and 8·1 per cent in group 2 (18 of 221)) increased in the presence of risk factors ($P < 0{\cdot}05$) and recourse to a non-resective procedure ($P < 0{\cdot}01$). After resection, malignancy is the only factor that determines an increase in mortality rates ($P < 0{\cdot}05$) (2·3 per cent in group 1 (four of 175) and 5·7 per cent in group 2 (ten of 175)).

In conclusion, age does not determine mortality rates as a result of elective colorectal surgery, even though it is a determinant factor in the increase in morbidity rates.

Stomach surgery on elderly patients for gastric carcinoma: frontiers in surgical treatment

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Surgical treatment for gastric carcinoma in patients aged over 70 years was evaluated by a retrospective clinical trial. From January 1989 to November 1992, 24 patients with a mean age of 78·2 years underwent operation for gastric carcinoma; cefotaxime was given as a perioperative antibiotic. Curative surgical therapy was achieved in 15 patients, while nine patients underwent palliative treatment. The procedures performed were: nine gastrectomies; seven high distal resections with reconstruction according to Billroth I in four patients and Billroth II in three patients; and two proximal resections with oesophagogastrostomy. Six patients underwent exploratory laparotomy.

The patients presented with a variety of concomitant diseases, as might be expected of this age group. Associated morbidity included arterial hypertension, cardiac insufficiency (II–III New York Heart Association), chronic coronary insufficiency, pulmonary insufficiency, diabetes mellitus II and renal insufficiency, in decreasing frequency. The mean value of preoperative risk evaluation according to the American Society of Anesthesiologists (ASA) was 2·9 for the group having gastrectomy, 2·8 for the group having gastric resection, and 3·0 for the group having exploratory laparotomy. In addition, three patients who underwent emergency operation because of perforation of the gastric tumour were classified ASA grade 4·0.

Mortality rates, early and late morbidity rates, and survival time were recorded. The early postoperative mortality rate (within 40 days) was 25 per cent. Two patients in the gastrectomy group died, including one having a palliative procedure. Four patients died in the exploratory laparotomy group, including two patients operated on as an emergency. Altogether, 18 patients were discharged a mean of 21·4 days after operation. After a mean follow-up period of 22·5 months, seven of the 15 patients with an R_0 resection have died within a mean time of 14·3 months after operation. Eight patients, including four with early gastric cancer, are alive after a mean interval of 17·2 months after operation.

In conclusion, surgical treatment of gastric carcinoma is realistic in elderly patients.

Surgical treatment of biliary disease in patients aged over 70 years

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A retrospective analysis of the results of 162 biliary operations performed during a 5-year period on patients aged over 70 years is reported.

Eighty-seven were elective operations (mortality rate 3·5 per cent) and 75 acute operations (mortality rate 6·2 per cent). During the same period 321 endoscopic retrograde cholangiopancreatographies (ERCPs) and 120 endoscopic sphincterotomies (ESs) were carried out in patients aged over 70 years, of whom 12 died (7·4 per cent).

The outcome of patients undergoing bile duct exploration was analysed. Three of ten patients undergoing a negative exploration died compared with five of 40 patients who underwent a positive exploration. To minimize postoperative morbidity and mortality, ERCP before elective surgery is recommended and, in selected cases, ES and stone extraction, leaving the callous gallbladder *in situ*.

It is considered that further study is necessary to determine whether urgent ERCP and, if bile duct calculi are diagnosed, ES with stone extraction, is justified before emergency operation on elderly patients.

Herniorrhaphy in the elderly

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All patients aged 80 years and over who were admitted with hernias during a 1-year period to the Department of General Surgery in Ringkoebing County, Denmark, entered a prospective study. Of 39 patients admitted, three refused operation. Among those remaining 23 were men and 13 women; median age was 84 (range 80–90) years. Fifteen cases (42 per cent) were admitted as emergencies.

Thirty-one patients had inguinal hernias, four had femoral hernias, and one an obturator hernia. All incarcerated femoral and obturator hernias contained non-viable intestine that required resection, while resection was necessary in only one of eight incarcerated inguinal hernias. All patients who required resection had a laparotomy.

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There were six major and two minor complications after 14 emergency operations, and one minor complication after 22 elective operations ($P = 0{\cdot}0007$). No association was found between coexisting disease and complications. Two patients died, both after emergency operation (14 per cent).

It is concluded that elective hernia repair can be performed safely even in the presence of serious coexisting disease; however, emergency hernia repair carries a high risk of complications even in the absence of coexisting disease.

Acute and elective surgery for colorectal cancer in patients aged over 75 years

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The records of 343 patients who underwent surgery for colorectal cancer were reviewed. Age, sex, site of tumour, clinical presentation, surgical management, histopathological stage and postoperative outcome were analysed retrospectively.

There were 102 patients (29·7 per cent) aged over 75 years (group 1) and 241 (70·3 per cent) under 75 years (group 2). The male to female ratio was similar in both groups. Elderly patients were admitted urgently in a greater proportion than were younger patients. A predominance of colostomy and Hartmann's procedure was noted in group 1 compared with group 2. In addition, septic complications more frequently followed both elective and emergency operations in the elderly group. The operative mortality rate was 10·7 per cent for group 1 and 2·9 per cent for group 2; total morbidity rates were 19·6 and 14·9 per cent respectively.

Despite advances in abdominal surgery and postoperative care, age remains a risk factor for outcome after surgery for colorectal cancer.

Cholecystectomy in patients aged 60 years or over: a comparison of open *versus* laparoscopic operation

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The aim of the study was to demonstrate the superiority of laparoscopic cholecystectomy *versus* open cholecystectomy in terms of morbidity and mortality rates, period of hospitalization and immobilization, time before restoration of bowel movements, and duration of procedure.

Patients undergoing elective laparoscopic cholecystectomy were compared prospectively with a historical group matched for age, sex, body mass index, associated medical illnesses and clinical presentation. The patients were aged ⩾ 60 years; all controls underwent routine cholangiography.

	Laparoscopic cholecystectomy ($n = 43$)	Control ($n = 34$)	P
Associated diseases	13	15	n.s.
Body mass index >27 kg m^{-2}	20	24	n.s.
Sex ratio (M:F)	6:37	8:26	n.s.
Mean(s.d.) age (years)	67·0(4·7)	67·5(3·4)	0·5
Duration of operation (min)	60·0(38·2)	90·0(35·2)	<0·001
Hospitalization period (days)	3·0(1·3)	9·5(2·8)	<0·001
Immobilization (h)	20·4(3·8)	72·0(15·2)	<0·001
Oral intake (h)	16·5(2·0)	48·0(7·9)	<0·001
Morbidity	2	7	<0·05

Laparoscopic cholecystectomy is a well tolerated, safe procedure compared with open cholecystectomy in patients aged ≥ 60 years. In this subgroup of patients laparoscopic cholecystectomy makes prophylactic cholecystectomy a feasible therapy for oligosymptomatic gallbladder disease and avoids the common policy of leaving the gallbladder *in situ* after endoscopic retrograde cholangiopancreatography.

Hernia

Interleukin 6 in laparoscopic *versus* open hernia repair

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Interleukin (IL) 6 initiates the acute-phase response to tissue injury. The magnitude of the systemic IL-6 response is related to the severity of surgery. Laparoscopic mesh hernia repair is a more invasive procedure than open herniorrhaphy as the operation requires intrusion into the peritoneal cavity and insertion of a polypropylene mesh. It was hypothesized that laparoscopic mesh hernia repair was physiologically more perturbing than open inguinal hernia repair. Twenty-two patients were prospectively randomized to three groups. Patients in group 1 (nine cases) had a laparoscopic inguinal hernia repair using a polypropylene mesh. Those in group 2 (ten cases) had an open hernia repair using a polypropylene mesh, while those in group 3 (three cases) had an open hernia repair using nylon darn. The plasma IL-6 level was measured before and at 5 and 24 h after surgery.

	Before surgery	After surgery	
		5 h	24 h
Laparoscopic mesh	6·4(1·7)	13·7(2·7)	13·1(3·1)
Open mesh	3·8(0·3)*	11·4(2·2)*	15·5(2·5)*
Open darn	2·9(0·1)*	7·5(1·8)*	7·8(1·9)*

Values are mean(s.e.m.) expressed in pg ml^{-1}. *P not significant *versus* laparoscopic mesh (Student's t test)

The advantages, if any, of laparoscopic over conventional hernia repair at present remain unproven. However, these results suggest that performing hernia repair laparoscopically is no more physiologically injurious than conventional inguinal herniorrhaphy.

Outpatient inguinal hernia repair

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The effectiveness of hernia repair in an outpatient setting was analysed and current approaches to hernia surgery in one unit are described.

A total of 500 consecutive inguinal hernias (429 primary, 71 recurrent) were repaired in 457 patients between January 1990 and October 1992. A 91 per cent follow-up rate at approximately 1 year was achieved. Patients were analysed with respect to many factors including type of operative procedure, anaesthesia, postoperative pain, time off work, recurrence, morbidity and mortality.

In all, 401 patients (88 per cent) were operated on in outpatient facilities. Most of the remaining 56 (12 per cent) were hospital inpatients who were undergoing surgery for other more serious complaints at the same time. Of the 457 patients, 281 (61 per cent) had local anaesthesia with 'Managed Anaesthesia Care'; 161 (35 per cent) received general, eight (2 per cent) spinal and seven (2 per cent) epidural anaesthesia. It was possible for 308 of the patients (67 per cent) to return to active life within 1 week. Complications were haematoma (ten, of which three were explored), neuralgia (nine), seroma (eight), fever of uncertain origin (one), laryngospasm after general anaesthesia (one), missed hernia in a nearby Pfannenstiel incision (one) and later development of a femoral hernia (one). There were no deaths, wound infections or recurrences.

In conclusion, through the coordinated efforts of surgeons, anaesthetists, patients and support personnel, excellent results can be obtained when inguinal hernias are repaired in outpatients.

Large inguinal hernias may be treated under local anaesthesia

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Surgeons are often reluctant to use a local anaesthetic technique when repairing large inguinal hernias. The purpose of this study was to test the efficacy of a local anaesthetic technique. The anaesthetic comprised 200 ml of 0·5 per cent lidocaine, injected subcutaneously in the groin and near the anterior superior iliac spine to cause a block of the genital branches of the ilioinguinal and genitofemoral nerves. The peritoneal sac was injected with lidocaine and not usually opened, but simply pushed back into the abdomen. All repairs were by the Shouldice technique. At the end of the procedure, the estimated size of the peritoneal sac, the presence of pain and the necessity of converting from local to general anaesthesia were recorded.

From January 1986 to December 1992, all patients having an inguinal hernia of >6 cm in diameter were included in the study. A total of 111 consecutive patients were defined as having a large hernia and operated on. Three patients were excluded, having had a general anaesthetic; among the remaining 108 cases (103 men, five women; mean age 59·8 (range 21–92) years) there were 60 right-sided hernias, 37 left-sided and 11 bilateral (of which four were also large), giving a total of 112 large hernias. The mean diameter of the sac was 8·6 (range 6–30) cm. Seven patients were operated on for recurrent large hernia. Nine patients described pain which necessitated repeated injection of local anaesthetic. No patient needed to convert from local to a general anaesthetic.

Audit of hernia repair with absorbable sutures

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A prospective study was conducted to determine whether inguinal hernia repair could be safely performed with absorbable suture materials over a 3-year period.

Analysis is available for 125 operations involving 119 patients. Mean follow-up was 21·8 (range 4–36) months, with 95 procedures monitored for more than 1 year. Shouldice repairs were performed in 94 per cent of cases. PDS and Vicryl accounted for 97 per cent and 98 per cent of sutures used for repair and skin closure respectively. Mean postoperative hospital stay was 2·1 (range 1–10) days, with no hospital infection and three haematomas. Review identified one infection, three further minor haematomas and five cases of wound or scrotal pain. There have been two recurrences.

Preliminary results suggest that hernia repair with absorbable sutures is comparable to traditional non-absorbable repair and warrants further investigation.

Herniography for occult hernia and groin pain

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A prospective study was performed to determine the value of herniography in the assessment of occult hernia and unexplained groin pain.

All patients presenting with a history of unexplained groin pain with no clinically apparent hernia underwent herniography using a standard technique.

To date, 28 patients (24 men) have been studied for up to 2 years. There were no complications from the procedure. Herniography identified an occult hernia in ten patients, confirmed subsequently at surgery. A further ten patients were deemed to have been spared surgery because of the herniogram. At follow-up, of those with a negative herniogram, no patient has developed a hernia and symptoms have resolved in 87 per cent. The clinical finding of a cough impulse was associated with a hernia in only 33 per cent of herniograms.

Herniography is concluded to be a safe and reliable diagnostic technique in the management of occult groin pain.

Laparoscopic *versus* open inguinal hernia repair

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To evaluate the selective merits of laparoscopic inguinal hernia repair and conventional open hernia repair a randomized study was conducted.

All patients were day cases randomized to a standardized open hernia repair under local anaesthetic or a laparoscopic hernia repair under general

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anaesthesia. Forty patients underwent open hernia repair (36 men, four women; median age 67 (range 23–81) years) and 40 laparoscopic repair (38 men, two women; median age 65 (range 20–80) years); ten of these patients had bilateral repairs.

Operating time for open hernia repair was 35 (range 25–70) min, for unilateral laparoscopic hernia repair 35 (range 30–80) min and for bilateral laparoscopic hernia repair 65 (range 45–80) min. Three open hernia repairs required conversion to general anaesthesia. One patient who underwent laparoscopic hernia repair was admitted for intra-abdominal bleeding and two who had open hernia repair required overnight admission for cardiac and psychological problems. Patients were discharged more quickly after open hernia repair (median time to discharge 142 (range 90–385) min) than laparoscopic hernia repair (median 220 (range 120–555) min; $P<0{\cdot}01$). Pain scores, activity scores and analgesia requirements were not significantly different during the 3 days after surgery in either group. Patients returned to work more rapidly after laparoscopic hernia repair (within 15·5 (range 5–57) days) than open hernia repair (30 (range 16–61) days). One hernia recurred, and there was one incidence of small bowel obstruction among patients who underwent laparoscopic repair.

It is concluded that both repairs can be performed successfully as day procedures although an earlier return to work is possible after laparoscopic herniorrhaphy.

Day-case inguinal hernia repair under local anaesthesia with sedation

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During a 1-year period 270 unselected patients with inguinal hernia underwent repair as a day case under local anaesthesia in combination with intravenous propofol sedation. There were 239 men and 31 women with an age range 11 to 78 years. Of the 300 operations performed, 171 (57 per cent) were Bassini–Shouldice, 90 (30 per cent) were Lichtenstein, 20 (7 per cent) were Ferguson and 19 (6 per cent) used the Prolene plug.

A total of 248 (92 per cent) of the patients were discharged the same day with an average length of stay in the unit of 4 h. Morbidity rate was 9 per cent. There was no mortality. The large majority of the patients (92 per cent) preferred the outpatient method; 73 per cent were followed by a home care service, and 27 per cent by telephone.

In conclusion, ambulatory hernia repair is possible and patient acceptability is high. Local anaesthesia with propofol sedation is safe and decreases fear in anxious patients.

Polytetrafluoroethylene patches for incisional hernia repair

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Abdominal incisional hernias are a continuing challenge because of their high recurrence rate. This study compared the use of polytetrafluoroethylene (PTFE) patches with conventional methods of hernia repair.

The recurrence-free rate was assessed in 25 patients who had undergone repair of incisional hernias following midline laparotomy using PTFE patches (1 mm) and sutures, and in 70 cases operated on within the past 2 years by different teams in the same institution using conventional techniques (simple closure with a double flap method).

The recurrence-free rate was estimated according to Kaplan and Meier. The impact of putative risk factors such as age, body mass index (BMI), defect size, number of previous hernia operations, and PTFE patch *versus* conventional repair was tested for significance using the Wilcoxon test and Cox multiple proportional hazards regression.

Recurrences were observed at follow-up in one PTFE case and in 41 patients after conventional repair. The recurrence rate after 18 months estimated according to Kaplan and Meier was 5 per cent for PTFE cases and 63 per cent for controls ($P < 0{\cdot}001$). The recurrences were diagnosed after a median interval of 8 months. Of the 42 recurrences, 39 (93 per cent) were observed within the first 10 months. Age, BMI, defect diameter and number of previous hernia operations were not significantly associated with an increased risk of failure. A relative risk of 19·9 for conventional repair compared with PTFE was estimated by multiple regression ($P<0{\cdot}001$). After correction for PTFE *versus* control none of the other variables studied was of additional significance in the multivariate model. A significant reduction of recurrence was observed within a median follow-up of 10 months of incisional hernia repair using PTFE patches and sutures. Almost all failures were encountered within 10 months of surgery. The short-term results indicate a significant improvement in the repair of incisional hernia by the use of PTFE patches and sutures compared with conventional surgery.

Short-stay surgery for inguinal hernia: a prospective study in 500 consecutive patients

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The feasibility of discharge within 48 h after hernia repair was evaluated in 500 unselected consecutive male patients scheduled for uncomplicated unilateral non-recurrent inguinal hernia repair. Fifty-nine patients were found unsuitable for early discharge on medical or social grounds. Of 411 patients suitable for short stay, 84 refused an early discharge and 42 were retained because of local or general complications. Discharge within 48 h was possible in 304 patients; 51 of these underwent day-case surgery. Physically undemanding employment, lower age, low medical risks and local anaesthesia were factors related to acceptance and success of short-stay surgery. These factors may be interdependent.

Expanded polytetrafluoroethylene darn repair of inguinal hernia: 5 years' experience

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The aim of the present study is to report 5 years' experience in the repair of inguinal hernia using a darn technique with an expanded polytetrafluoroethylene (ePTFE) suture. A total of 184 patients, 23–72 (mean 52·3) years old, underwent elective lateral inguinal hernia repair by a single consultant surgeon, 68 for direct and 116 for indirect inguinal hernias. The 'ePTFE darn' technique is the 'nylon darn' method (Moloney's technique) applied and modified in two areas; instead of the nylon suture, a monofilament suture is used, made from ePTFE. The transversalis fascia repair is reinforced by an ePTFE suture stitched in an interlacing manner, after reinforcement of the internal ring by the same suture. After operation suture sinus formation, deep sepsis and discharging haematoma was observed in one patient (0·5 per cent), superficial wound infection healed without complication in four patients (2·2 per cent) and there was an overall recurrence rate of 1·6 per cent (three patients). None of the patients developed symptoms of inguinal nerve entrapment, sinus formation or testicular swelling. The average postoperative hospitalization was 3·7 days. The ePTFE suture was tolerated well by the tissues, in all cases, with no local reaction. All patients were followed for 5 years after the operation.

It is concluded that, in ePTFE darn technique, the use of ePTFE suture is well tolerated by the tissues. The reinforcement of the transversalis fascia, stitched in an interlacing manner with the same material, reduces the recurrence rate.

Hydatid disease

Modification of capsule dome excision in the surgical treatment of hydatid disease of the liver: 15 years' experience

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Surgical treatment of hydatid disease of the liver still presents several serious technical problems. Postoperative biliary fistula and infection are the main causes of prolonged hospitalization and are the most frequent cause of morbidity in this disease. Reported here are 158 cases of hydatid disease of the liver (97 involving the right, 23 the left lobe of the liver, 15 at the hilum, 61 with multiple locations), that were treated surgically during the past 15 years. The technique in use included: (1) wide excision of the dome of the capsule; (2) identification of open biliary ductules (which was assisted by the injection of water under pressure, through the cystic or common bile duct after cholecystectomy); and (3) avoidance of a drainage tube whenever possible.

The mean postoperative hospital stay was 8·7 days for 57 cases where no drainage tube was used and 15·4 days for 97 cases where a drainage tube was used. There were two (1·3 per cent) postoperative deaths and 15 (9·5 per cent) complications related to the operative procedure (biliary leakage in three cases, infection in nine, and gastric paresis in three).

It is concluded that this technique is efficient, easy to perform and a safe surgical treatment for hydatid disease of the liver, with major advantages compared with the standard techniques in use.

Surgical treatment of hydatid liver disease

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Surgical treatment of hydatid liver cysts is controversial. Experience with 189 patients is reported. Of these, 58 patients had complicated cysts before operation and the postoperative complication rate in these patients (53 per cent) was higher than in the remaining 131 patients (12·9 per cent) ($P < 0{\cdot}001$). Patients with uncomplicated cysts before operation were divided into four treatment groups.

Group	No.	Treatment	Complication rate	Mean hospital stay (days)
1	24	Hepatectomy or cystopericystectomy	2 (8)	10·1
2	45	Omentoplasty or primary closure	3 (7)	9·7
3	41	Tube drainage of the narrowed pericyst	9 (22)	19·1
4	21	Simple tube drainage	3 (14)	17·8

Values in parentheses are percentages

The complication rate in groups 1 and 2 was higher than in the other two groups ($P < 0{\cdot}008$), but there was no statistical difference in the complication rates between groups 1 and 2 ($P = 0{\cdot}88$) and groups 3 and 4 ($P = 0{\cdot}36$).

In conclusion, morbidity rates in hydatid cyst surgery are related to preoperative complications. Tube drainage should be abandoned if possible, and radical resections are not better than omentoplasty or primary closure. If the pericyst cavity is drained, it should not be narrowed.

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Infection

Nosocomial infection after oncological surgery: results of a prospective study

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A prospective study investigating the incidence of nosocomial infection was conducted for oncological surgery. A total of 90 patients underwent a variety of surgical procedures.

The overall incidence of nosocomial infection was 61 per cent (55 infections) during the study period. This high rate is related to infections of varying seriousness. The most common infections occurred in the surgical wound (20 per cent), respiratory tract (19 per cent), urinary tract (10 per cent) and bloodstream (9 per cent).

The incidence for surgical wound infection was: clean (14 per cent), clean contaminated (18 per cent), contaminated (36 per cent) and dirty (12 per cent). This overestimates the rate for clean and clean contaminated procedures since only high-risk patients are usually hospitalized in the intensive care unit. The rate of nosocomial infection related to contaminated procedures remains high.

The ω-3 fatty acids increase myocardial contractility during endotoxic shock in the rat *in vitro*

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During Gram-negative sepsis there is myocardial depression believed to be mediated by the release of endotoxin. Dietary fish oils have attracted considerable interest in this context since their constituent ω-3 lipid fraction can modulate the release of cytokines and prostaglandins. Fifty-two Sprague–Dawley rats were fed 20 per cent beef tallow (saturated lipid) or 20 per cent fish oil for a period of 5 weeks after which they were infused with either 1 mg kg^{-1} endotoxin or saline control over 24 h. The animals were then killed and the force of contraction of the atrial heart muscle measured in response to the β_1-agonist isoprenaline in an *in vitro* organ bath. The ventricular portion of the heart was frozen and used later to measure the β_1 receptor density (B_{max}) and affinity (K_d) using radioligand binding. The *in vitro* bath data were analysed using curve-fit techniques to find the maximum response and the dose of isoprenaline inducing half maximum response (EC_{50}).

Endotoxin induced myocardial depression as illustrated by left shift in the dose–response curves (increased mean(s.e.m.) EC_{50}) in both endotoxin-treated groups (3·38(0·46) and 3·52(0·58) μg *versus* 1·79(0·35) and 1·73(0·42) μg, $P = 0·0058$ endotoxin *versus* saline, two-way ANOVA). In addition there was a significant increase in the maximum response to β_1-stimulation in the fish oil-fed animals (0·46(0·05) and 0·50(0·04) g *versus* 0·40(0·04) and 0·37(0·04) g, $P = 0·042$ fish oil *versus* beef tallow, two-way ANOVA). While there was no significant difference in B_{max} in the experimental groups, K_d was higher in the fish oil-fed animals (41(2) and 45(3) pM *versus* 40(3) and 40(3) pM, $P < 0·05$ fish oil *versus* beef tallow, two-way ANOVA).

The data suggest that a fish oil diet may be useful in the treatment or prophylaxis of septic shock where reduced responsiveness to β_1-adrenergic stimulation is a factor.

Endotoxin causes myocardial depression in the rat while causing β-adrenergic receptor up-regulation

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The myocardial depression of septic shock has a major impact on survival. Endotoxin is believed to mediate myocardial depression by impairing response to adrenergic stimulation. This study measured cardiac β-receptor (βIR) density in a low-dose endotoxin model of sepsis, and observed pulse and contractile response to isoprenaline (ISO) stimulation.

A total of 30 Sprague–Dawley rats were infused with 1 mg kg^{-1} of endotoxin (EN) or normal saline (NS) for 24 h via the jugular vein. The animals were then killed and the atria suspended in an *in vitro* organ bath. The ventricles were immediately frozen in liquid nitrogen for later crude plasma membrane preparation. The force of contraction and pulse rate were measured in response to increasing doses of ISO added to the bath. Ventricular membranes were bound with ^{125}iodocyanopindolol and the number (B_{max}) and affinity (K_d) of the βIR for each heart computed by Scatchard analysis.

ISO (μg l^{-1})	0	2·5	5	10	20
EN force (g)	0·38(0·03)	0·57(0·05)*	0·69(0·05)*	0·79(0·05)*	0·79(0·05)*
NS	0·46(0·02)	0·85(0·05)	0·97(0·05)	0·98(0·05)	0·97(0·05)
EN pulse	338(7·1)	423(10)	453(9·8)	476(9·7)	498(9·8)
NS	321(4·8)	416(9·4)	448(8·1)	471(7·1)	496(5·9)

Values are mean(s.e.m.). * $P < 0·05$ (EN *versus* NS, Student's *t* test)

There was a reduction in stimulated force of contraction after endotoxin. In contrast, the stimulated pulse rate was almost entirely unaffected by endotoxin. There was a significant increase in receptor density in the endotoxic animals (EN 84·6(5) fM g^{-1} *versus* NS 70·4(3) fM g^{-1}, $P = 0·04$), while K_d was no different. Thus, the cardiac depression was not explained by a reduction in receptor number. This makes receptor desensitization an unlikely cause of the myocardial depression found in this model. Indeed, there seems to be an up-regulating influence during endotoxin administration.

Respiratory infection following major surgery: a prospective audit

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Respiratory infection is known to be common following major surgery, but there have been few studies of this problem in the past 20 years. A prospective audit of postoperative complications following major surgery in a unit with a high proportion of complex cases was carried out. A total of 443 patients were studied: complications occurred in 128 (28·9 per cent) cases and there were 39 deaths (8·8 per cent). Respiratory infection accounted for 71·1 per cent of all complications and 38 per cent of deaths. Respiratory problems were the major reason for admission to the intensive care unit. Age, smoking, emergency surgery, severity of operation, use of a nasogastric tube, blood loss and poor preoperative physiological scores were significant risk factors. The use of respiratory stimulants had no protective effect. Laparoscopic surgery was associated with significantly fewer respiratory infections.

Pathogenic organisms were cultured in 74 cases, of which the commonest was *Haemophilus influenzae*. Infection occurred usually within 72 h of operation or when the patient resumed oral fluids.

Respiratory infection is the commonest complication of major surgery and accounts for a large proportion of postoperative deaths. It may be possible to reduce the incidence by reducing the use of nasogastric tubes. There may also be a place for narrow-spectrum antibiotic prophylaxis.

Perineal gangrene

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Perineal gangrene (PG) is still a serious infection despite aggressive surgery and modern antibiotics. In all, 21 patients (six women, 15 men) with a median age of 65 (range 44–85) years have been treated by the authors over the past 10 years, 19 of whom presented as emergency cases and two following postoperative complications. Routine and repeated bacteriological samples were taken until proven bacteriological cure. Aggressive surgical treatment was performed in all cases, although only two patients needed a colostomy. The most commonly used antibiotics were combinations of gentamicin and metronidazole or cefotaxime and metronidazole. The main causes of PG in the present series were anorectal

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infection (nine cases) and urological disease (seven). Pathological conditions were associated with 90 per cent of cases of PG, the most prevalent being diabetes mellitus (72 per cent of cases) and peripheral vascular disease (18 per cent). The bacteriological study identified mixed infections in 90 per cent of cases. Bacteriological cure was proven in 72 per cent of the patients between days 7 and 15 after onset. Six patients (29 per cent) died, four from septic shock and two from pulmonary embolism. The mean(s.d.) hospital stay was 28(12) days. PG is a severe condition that requires early and extensive surgery, combined antibiotic therapy, thromboembolic prophylaxis and close follow-up.

Interleukins 6 and 8 are prognostic indicators of mortality in severe intra-abdominal sepsis

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Proinflammatory cytokines have been implicated in the adverse sequelae of patients with severe intra-abdominal sepsis (IAS), which is still responsible for a significant number of deaths and the outcome is not readily predictable. The Acute Physiology and Chronic Health Evaluation (APACHE) II score of predicting outcome has several drawbacks.

This study aimed to compare the APACHE II score with levels of plasma cytokines and circulating endotoxin to predict outcome of severe IAS. A total of 41 patients were studied within 24 h of onset of the sepsis syndrome and at serial time points. There were 19 deaths (46 per cent). At enrolment, raised plasma interleukin (IL) 6 levels were detectable in all patients with sepsis and were >2000 pg ml^{-1} in 15 of the 19 who died (χ^2 = 23·7, P<0·001). IL-8 levels were >2000 pg ml^{-1} in 11 of those who died (χ^2 = 11·2, P < 0·001). The specificity of plasma IL-6 and plasma IL-8 levels in predicting mortality with a cut-off at 2000 pg ml^{-1} was 95 and 91 per cent respectively and these are better predictors of adverse outcome compared with the APACHE II score. Levels of tumour necrosis factor, IL-1β and endotoxin did not correlate with death. Raised levels of plasma IL-6 and IL-8 not only clearly demonstrate an important role in sepsis but if >2000 pg ml^{-1} relate to a poor prognosis.

IL-6 and IL-8 determination on a routine basis may help in planning future strategies to decrease the mortality associated with sepsis.

Septic shock in rats: tumour necrosis factor–prostaglandin E_2 modulation under intravenous somatostatin perfusion

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The objective of this study was to determine whether somatostatin can modify the production of tumour necrosis factor (TNF) and plasma prostaglandin (PG) E_2 in septic shock.

Forty male Wistar rats of mean(s.d.) weight 360(10) g each received 2·2 × 10^{-7} units bacille Calmette–Guérin intraperitoneally. After 15 days, 0·5 mg kg^{-1} lipopolysaccharide B (*E. coli* 0127:B8) was given intravenously. Twenty rats were perfused intravenously with physiological serum at 0·1 ml h^{-1} for 24 h, the other 20 with intravenous somatostatin at 2 μg h^{-1}. Animals were killed in groups of ten (five from each experimental arm) at various times. In each rat, measurements were made of TNF and PGE_2, and histological analysis was performed.

All animals given physiological serum developed diarrhoea. Histological examination showed slight oedema of the lamina propria with an increased number of cells. Rats given intravenous somatostatin did not develop clinical or histological changes.

	Time after treatment (h)			
	1·5	3	6	24
TNF				
Serum	2220(694·5)	820(253·7)	0	0
Drug	770(101·9)*	0	0	0
PGE_2				
Serum	388·7(50·9)	304(31·8)	160·6(29·4)	51·8(7·7)
Drug	2152·8(1156·9)*	1365·3(591·6)*	676·3(330)*	82(22·5)

Values are mean(s.d.). *P < 0·001 (somatostatin *versus* serum)

Somatostatin inhibits the production of TNF in this animal model of septic shock, and increases levels of PGE_2.

Laparoscopic procedures

Pulmonary function after laparoscopic and open cholecystectomy

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Upper abdominal surgery causes postoperative changes in pulmonary function. Few studies have been reported concerning pulmonary function after laparoscopy. Two groups of patients with gallstones treated randomly by either laparoscopic cholecystectomy (LC) ($n = 25$) or by open cholecystectomy (OC) ($n = 25$) were compared. Each group was homogeneous for age, sex and American Society of Anesthesiologists status. The technique of anaesthesia was identical in all patients. Respiratory function was analysed by spirometry, clinical examination and chest radiography. Forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume in 1s (FEV$_1$), mid-expiratory flow at 50 per cent of FVC (MEF$_{50}$), and mid-expiratory flow at 25 per cent of FVC (MEF$_{25}$) were assessed before and after operation until these parameters returned to normal values. In the LC group the ventilatory data remained abnormal for not more than 48 h. In the OC group it was often not possible to perform respiratory evaluation in the first 48 h because of discomfort and it took 5–7 days for respiratory function to return to normal.

These results demonstrate that pulmonary function after laparoscopy recovers faster than after laparotomy.

How minimally invasive is laparoscopic cholecystectomy?

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Postoperative serum cortisol, growth hormone and insulin responses were determined in two groups to determine the extent of surgical stress induced by open ($n = 20$) and laparoscopic ($n = 20$) cholecystectomy. The groups were matched for age, sex ratio and duration of surgical procedures. The group undergoing open cholecystectomy revealed significant elevations of serum cortisol, growth hormone and insulin levels 8 h after surgery ($t = 1{\cdot}94$, $P = 0{\cdot}03$; $t = 1{\cdot}8$, $P = 0{\cdot}03$ and $t = 2{\cdot}7$, $P = 0{\cdot}005$). In the group undergoing laparoscopic cholecystectomy, only the increase of growth hormone was significant ($t = 2{\cdot}01$, $P = 0{\cdot}03$). In both groups cortisol and growth hormone levels gradually returned back to control values 48 h after surgery. The increased insulin levels persisted in both groups 24 and 48 h after surgery. It is concluded that acute surgical stress induced by open cholecystectomy is more severe than that caused by laparoscopic surgery as reflected by serum hormone determinations. The hormonal convalescence rate was similar for both groups. It appears that laparoscopic cholecystectomy is minimally invasive as far as the hormonal responses are concerned.

New technologies in laparoscopic cholecystectomy: ultrasonography, Cusa and argon coagulator

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Laparoscopic cholecystectomy represents the 'gold standard' for treatment of symptomatic gallstones and gallbladder polyps. Increasing experience with this technique has broadened the indications to include acute cholecystitis and chronic sclerotic cholecystitis. In such conditions pathological modifications of the anatomy of the biliary tree could enhance the risk of injuring the common bile duct during isolation of the cystic duct, or that of bleeding from the hepatic bed or from an unidentified cystic artery.

In performing simple cholecystectomy the presence of anatomical variations of the biliary and arterial trees and the possibility of choledochal gallstones, descended from the cystic duct during laparoscopic manoeuvres, should be considered. Laparoscopic cholangiography is not widely performed due to the potential risk of further choledochal injuries and the long time usually required to perform this procedure. The laparoscopic 10-MHz Aloka probe is used to perform safe, rapid and reliable ultrasonographic examination of the triangle of Calot and hepatoduodenal ligament during laparoscopic cholecystectomy. The cystic duct, cystic artery and common bile duct are evaluated before and after gallbladder removal, to exclude potential hazards in the biliary tree and to verify the absence of residual choledochal stones.

The Cusa dissector facilitates the careful anatomical preparation of the cystic duct and cystic artery. Accurate dissection of the gallbladder from the hepatic bed is also performed with this probe such that even minimal vessels are accurately spared. The argon laser is then used to allow a safer haemostasis of the liver surface.

The high cost of this technique is outweighed by the absence of even minimal bleeding and by the safety in sparing the hazard of biliary tree injury.

Laparoscopic splenectomy

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Seven patients were treated by laparoscopic splenectomy for idiopathic thrombocytopenic purpura between January and December 1992. Two were human immunodeficiency virus seropositive.

There were two men and five women with an average age of 38 years. All presented a refractory or relapsing idiopathic thrombocytopenic purpura (average platelet count 19 500 mm^{-3}). The splenic volume was normal in all cases.

Before operation, pneumococcal vaccine, human immunoglobulins and platelets were given to raise the number of platelets (average 111 800 mm^{-3} before operation). Five trocars were used. The peritoneal layer covering the hilum of the spleen was divided with a coagulating hook. The short gastric vessels were isolated, clipped and divided. The hilar artery and vein were divided with an Endo-GIA stapler in the first case and ligated in the six other cases. Removal of the spleen was possible in a plastic bag that was partially exteriorized. The spleen was crushed with a forceps and removed piecemeal or aspirated with a powerful suction device. A drain was left in the upper quadrant in the first six patients.

No conversion to laparotomy was necessary. There were no peroperative or postoperative complications. Average operating time was 4 h. Average blood loss was estimated at 262 ml. Active bowel sounds were present and oral intake was allowed on the first day. Drains were removed on the second day (average drainage was 128 ml). The platelet count was normal on the second day (average 258 000 mm^{-3}). Mean hospital stay was 3 days. No complications were seen after 1 month of follow-up.

In conclusion, laparoscopic splenectomy is feasible for spleens of normal volume. This approach is to the patients' benefit.

Prospective study of laparoscopic proximal gastric vagotomy

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Between April 1992 and February 1993, 30 consecutive patients (26 men and four women, mean age 38 (range 19–65) years) underwent proximal gastric vagotomy (PGV) without pyloroplasty by strictly laparoscopic means. The mean body mass index was normal at 22·6 (range 17–30) kg m^{-2}. No patient had associated systemic disease. Two patients had undergone previous gastric surgery (one pyloroplasty and one closure of a perforated ulcer). Six others had undergone lower abdominal procedures. Twenty-three patients were operated on electively, because of chronic ulcer disease alone (16 cases) or associated with gastro-oesophageal reflux disease (seven). Seven patients were operated on as an emergency for perforated peptic ulcer. Thirteen patients underwent fundoplication during the same procedure; seven underwent associated perforated ulcer closure and one cholecystectomy. The procedure consisted of selective severance of all fibres originating from Latarjet's nerve supplying the lesser gastric curvature, cephalad of the crow's foot, care

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being taken not to injure the main trunk. Dissection included the distal 8-cm length of oesophagus in all cases.

There was no perioperative mortality or morbidity. There were no conversions to open laparotomy. Mean operative time was 172 (range 90–270) min. Postoperative stay was 2 days in the elective group and 5 days in the emergency group. This difference was due to prolonged intravenous antibiotic therapy and gastric suction in the perforated ulcer group (5 days *versus* 1 day in the elective group).

During follow-up (range 1–10 months), 14 of 17 patients were symptomless (Visick grade 1 or 2). Three patients were staged as Visick 3, because of ulcer pain (one case), heartburn (one), or regurgitation (one). Postoperative gastroscopy was performed on 11 patients, eight being normal. In one patient, gastritis and symptomless oesophagitis was observed, one had a healing duodenal ulcer and one an erosion on the lesser curvature due to a migrated clip.

It is concluded that laparoscopic PGV is feasible and carries a low morbidity rate. It can be combined with the laparoscopic treatment of perforated ulcer. However, long-term functional results must be awaited.

Preliminary results of laparoscopic repair of perforated duodenal ulcer

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Laparoscopic repair of perforated duodenal ulcers offers several advantages. Laparoscopy confirms the diagnosis, and the absence of an upper abdominal incision in a frequently frail and elderly group of patients allows early mobilization, reducing postoperative complications.

A series of ten consecutive patients with perforated duodenal ulcer underwent operation using a laparoscopic technique. Mean age was 62 years. All patients had a laparoscopic omental patch repair (sutured or stapled) with peritoneal washout.

Repair	n	Operating time (min)	Hospitalization (days)
Stapled	3	25*	5
Sutured	7	110	6

Values are means. $^*P < 0·01$ (Student's t test)

There were no deaths. One patient developed a chest infection after surgery. Early mobilization and discharge was a notable feature.

In conclusion, laparoscopic repair of perforated duodenal ulcer is a safe and effective technique. The stapled method is rapid and obviates the requirement for tedious and time-consuming intracorporeal or extracorporeal suturing.

Shoulder pain after laparoscopic surgery: reason and consequence

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After laparoscopic surgery, patients occasionally describe a transient right shoulder pain of variable intensity. The aim of this study was to evaluate the role of the residual pneumoperitoneum and its consequences on postoperative pulmonary function. At the end of the surgical procedure, the pneumoperitoneum was blown out by careful manual compression of the abdomen. Abdominal radiography was performed on the first day after surgery with patients in an upright position. The area of pneumoperitoneum in the right and left subdiaphragmatic spaces was measured. The shoulder pain was assessed by means of a questionnaire. All patients had pulmonary function tests on the day before surgery, and the first postoperative day.

From March 1992 to November 1992, 24 patients (13 women, 11 men; mean age 50·1 (range 21–80) years) having laparoscopic surgery, entered the study. On the first postoperative day, four patients (group 1) experienced right shoulder pain (three also had left shoulder pain); 20 patients (group 2) had no pain. The mean (range) surface of the pneumoperitoneum was 16·25 (14·29–21·87) cm^2 in group 1 and 0·77 (0–5·94) cm^2 in group 2 ($P = 0·0048$, t test). There was a mean decrease in forced vital capacity on the first postoperative day of 37·1 per cent (4·04 falling by 1·49 litres) in group 1, but only 16·4 per cent (3·4 falling by 0·55 litres) in group 2; however, this difference is not statistically significant ($P = 0·16$, t test).

It is concluded that after laparoscopic surgery the shoulder pain is related to a residual pneumoperitoneum and is probably responsible for a postoperative decrease in forced vital capacity.

Intraperitoneal onlay mesh technique for laparoscopic groin herniorrhaphy: preliminary results in 123 cases

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Primary groin hernia repair using a prosthetic mesh to create a new inguinal floor is an increasingly popular technique. In the present study a transperitoneal laparoscopic approach was used; results are presented which evaluate operating time, postoperative pain, length of hospital stay and work interruption.

Between May 1992 and February 1993, 123 groin hernias have been repaired in 116 patients. The technique involves laying a polypropylene mesh over the myopectineal orifice (after reduction of the sac and separation of the vas and spermatic vessels) and securing it in place with staples. In total, 100 men and 16 women (mean age 50 (range 19–85) years) have been treated. In seven cases, the hernia was bilateral. The hernia was inguinal in 119 cases, femoral in four and both inguinal and femoral in two. Inguinal hernias were categorized by the Nyhus classification: 61 type II, 49 type IIIA, four type IIIB, and seven type IV.

The mean operating time was 73 (range 25–180) min. Four conversions to open surgery were performed: two because of bowel adherence in the sac and two because of intolerance of the pneumoperitoneum under an epidural anaesthetic. There were no operative complications. Forty-five patients required no postoperative analgesia; 50 needed analgesics only for 24 h after surgery. Mean hospital stay was 3·3 (range 0–12) days. One patient was readmitted 14 days after operation because of an infected haematoma. To date, 92 patients have been examined with a minimum follow-up of 1 month; all have normal activity including 25 heavy-duty workers.

In conclusion, laparoscopic groin hernia repair seems to be a reliable, safe and easily reproducible technique. Postoperative comfort should allow early recovery of professional activity. Even though results are encouraging, a longer follow-up is necessary fully to evaluate the effectiveness of this approach.

Acute-phase response after laparoscopic and open cholecystectomy

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The aim of this work was to assess the acute-phase alterations of blood lymphocyte subsets, plasma proteins and selected hormones in patients undergoing laparoscopic cholecystectomy (LC) and open cholecystectomy (OC) to compare the effects of surgical trauma resulting from the two procedures.

A total of 57 well nourished candidates for cholecystectomy for uncomplicated cholelithiasis, with no indication for common bile duct exploration, were prospectively randomized into two groups undergoing either LC (n = 30) or OC (n = 27), using the same type of general anaesthesia. In each patient blood samples were drawn before operation and at various time intervals after surgery to determine the concentration of lymphocyte subsets CD3, CD4, CD8, OKDR and the plasma levels of C-reactive protein (CRP), cortisol and prolactin.

The duration of operation and general anaesthesia was similar in the two patient groups. The mean(s.d.) postoperative hospital stay was shorter after LC than after OC (3·1(0·5) *versus* 7·1(1·6) days; $P < 0·001$). After OC a significantly greater ($P < 0·05$) depression of blood CD3 and OKDR counts was found, as compared to LC. Moreover, OC patients showed a significantly greater postoperative acute-phase increase of plasma CRP

($P<0{\cdot}001$), of cortisol ($P<0{\cdot}05$) and of prolactin blood levels ($P<0{\cdot}001$).

The significantly lower acute-phase responses of immunological and metabolic parameters observed after LC support the concept that the laparoscopic procedure is less traumatic.

Laparoscopic surgery for benign colorectal disease: a multicentre prospective study

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Laparoscopic colectomy appears more controversial than other laparoscopic procedures. The aims of this prospective study were to evaluate the feasibility of laparoscopic colorectal surgery in benign disease, and to assess the operative and early postoperative outcome in a homogeneous group of patients.

Between May and November 1992, 35 patients (24 women, 11 men) were included in the study. Mean age was 50 (range 17–81) years. Nineteen patients had undergone previous abdominal surgery. Indications included Crohn's disease (11 patients), colonic polyps (nine), complications of diverticulosis (nine), colonic inertia (four) and sigmoid volvulus after initial decompression (two). In six patients a conversion to open laparotomy was performed (one with abscess, one adhesion, one cancer, one Crohn's fistula, one obesity and one for anatomical reasons).

Laparoscopic operations performed included sigmoid colectomy (nine), ileocolic resection (seven), left hemicolectomy (five), right hemicolectomy (four), total colectomy with ileorectal anastomosis (three), and colotomy for polypectomy (one). The specimen was removed through a small abdominal incision (mean 5 (range 3–10) cm length) in 26 cases and there were three transanal extractions of the resected colon. The mean length of specimens was 39 (range 15–105) cm. Anastomosis was performed either extracorporeally (16 patients) or intracorporeally (13). There was no mortality, while morbidity rate was 26 per cent. Mean time to pass flatus was 3 (range 1–7) days and to resume a soft diet 5 (range 3–7) days. The mean hospital stay after surgery was 9 (range 5–23) days.

These results indicate that laparoscopic colorectal surgery is safe and feasible in selected patients, even when previous abdominal surgery has been performed.

Laparoscopic highly selective vagotomy for duodenal ulcer disease

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The great success of medical ulcer treatment argues for conservative therapy, but continuous long-term drug therapy requires patient compliance and is expensive. Therefore a minimally invasive, acid-reducing operation may have a place in ulcer management. Highly selective vagotomy (HSV) has been evaluated in large studies over a long period. The results are acceptable, with low rates of complications and the absence of bowel resection or opening being powerful arguments. Laparoscopic HSV is a difficult operation.

Fifteen patients with good results are presented. Operation time was from 2·6 to 3·75 h. On the second day after operation the patients were pain-free and ate normally. Normal leisure activities were resumed after 1 week as a rule. There were no major complications, only two infected trocar sites. Acid output reduction to 30 per cent of normal was shown in six patients 6 months after operation, but this is too short to assess long-term effects. Physiologically, HSV has minimal effects on gastric vagal innervation, and does not cause gastric outlet obstruction. There is no place for truncal vagotomy in the therapy of uncomplicated duodenal ulcers. The Taylor procedure may only be a compromise for difficult laparoscopic cases. Precisely performed laparoscopic HSV with cutting of the nervus criminalis on the oesophagus and the vagal branches up to the crow's foot has an acid output reduction comparable to conventional surgery. Closure of the serosa of the lesser curve prevents adhesions, allowing subsequent fundoplication for reflux. Laparoscopic HSV is a realistic alternative to long-time drug therapy, being cheaper and a permanent cure.

Laparoscopically assisted colorectal surgery

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The role of laparoscopic colorectal surgery is currently being evaluated. Fourteen patients (median age 57 years) underwent laparoscopically assisted colorectal surgery. The operations performed were: right hemicolectomy (Crohn's disease, $n = 4$; carcinoma, $n = 4$); left hemicolectomy (carcinoma, $n = 2$); subtotal colectomy (colitis, $n = 1$; colonic inertia, $n = 1$); and abdominoperineal excision ($n = 2$). In all cases the colon was mobilized laparoscopically and delivered through a small incision for resection and/or anastomosis. In one patient with caecal carcinoma laparoscopy was converted to laparotomy because of anatomical uncertainty. Median duration of surgery was 135 min and median postoperative hospital stay 5 days. In all the patients with carcinoma, excision margins were clear; a median of eight lymph nodes were excised. These data suggest that laparoscopic surgery will play an increasing role in the treatment of colorectal disease. However, the outcome of surgery for colorectal malignancy will be apparent only at follow-up.

Laparoscopic inguinal hernioplasty with a reinforced polyester prosthesis

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Laparoscopic hernioplasty has been performed for 3–4 years. Reports of complications such as nerve entrapment, intestinal obstruction and recurrence are numerous. An attempt has been made to obviate these problems by using a different type of prosthesis made of a soft reinforced polyester mesh which has proven inertness. It contains a frame of superelastic metal (Nitinol), which speeds up the placement procedure and also provides stability. Circumferential fixation is not necessary, one- or two-point fixation being sufficient.

Between 1 January 1992 and 28 February 1993, 85 patients with 108 hernias were treated using this new prosthesis. No cases of nerve entrapment were encountered. There was no clinical evidence of intraperitoneal migration of the mesh. One patient had a clinical recurrence. During the same period, 41 patients with 61 hernias were treated using a preperitoneally placed polypropylene prosthesis, stapled on its circumference, care being taken not to place any staples caudad of Poupart's ligament. Again, there was one recurrence. However, three cases of nerve entrapment and two of intraperitoneal migration with subsequent small bowel obstruction (at 4 and 6 months) were encountered. Five reoperations were necessary to resolve these complications.

This experience indicates that laparoscopic inguinal hernioplasty using a reinforced self-expanding polyester mesh has a low complication rate.

Laparoscopic appendicectomy: advantages over open operation

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Recent reports have suggested that laparoscopic appendicectomy (LA) confers some advantages over open appendicectomy (OA). In a prospective study results in the first 75 patients undergoing LA were compared with those in the last 50 patients who underwent OA. All patients had signs and symptoms suggesting acute appendicitis. The mean age was 30 (range 9–74) years. Postoperative recovery, complications and return to normal activities were compared in the two groups.

	LA ($n = 75$)	OA ($n = 50$)
Operating time (min)	70	46
Hospital stay (days)	2·8	4·2
Complications	10	7
Negative rate (%)	24	27
Return to normal activity (weeks)	2·3	4·2

Although the overall complications were similar in the two groups, three patients developed major postoperative complications after LA. These included small bowel perforation due to a diathermy injury, right iliac fossa haematoma and small bowel obstruction. Hospital discharge was significantly shorter after LA. Follow-up showed a shorter bed stay at home and faster return to normal activity after LA.

In conclusion, these data demonstrate that LA is superior to OA in terms of hospital stay and return to normal activity, but the potential for significant postoperative complications is a concern.

Laparoscopic *versus* open cholecystectomy

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Two groups of 300 patients, who had undergone laparoscopic or open cholecystectomy, were studied to compare the effectiveness and complications of the two procedures. The groups were not randomized. Clinical findings in both groups were similar (laparoscopic and open cholecystectomy respectively): recurring biliary colic 59·6 and 50·7 per cent; chronic cholecystitis 28·0 and 34·7 per cent; gallbladder hydrops 7·6 and 8·9 per cent; and empyema 4·8 and 5·7 per cent. No patient in either group required reoperation. Bile duct injury occurred in one patient from each group. Postoperative bile leak affected one and four patients undergoing laparoscopic and open procedures respectively. Wound infection occurred in two patients after laparoscopic and nine after open cholecystectomy. There were no pulmonary complications after laparoscopic cholecystectomy but 19 per cent after open cholecystectomy. Average hospital stay was 2·1 and 9·6 days after laparoscopic and open procedures respectively.

It is concluded that laparoscopic cholecystectomy is a safe procedure, has a low morbidity rate and decreases the cost of treatment. Laparoscopic cholecystectomy should replace open cholecystectomy.

Laparoscopy in right lower quadrant pain in young women: a controlled study

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Of 187 patients presenting during 1 year with abdominal pain, 66 were young women with non-specific right lower quadrant pain.

These patients were randomized in two groups of 33 patients each. One group underwent a diagnostic laparoscopy, the other group had conventional diagnostic investigations only. Laparoscopy enabled a diagnosis to be made in 97 per cent of cases and the simultaneous treatment of acute appendicitis in two-thirds of the patients in that group. The conventional group had only a 28 per cent accurate diagnosis. The mean hospital stay of the laparoscopy group was significantly less than that of conventionally treated patients ($P = 0·01$).

Arguments of cost–efficiency and of healthcare favour laparoscopy as the investigation of first choice in non-specific abdominal pain in young women.

Laparoscopic treatment of small bowel obstruction: results in 25 patients

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Laparoscopic treatment of small intestinal obstruction could be associated with immediate advantages and it might be expected that the recurrence rate will be decreased because of the diminution in the number of wound scars.

Between September 1989 and September 1991, 25 patients (16 men and nine women; mean age 53·8 years) underwent laparoscopy for acute small intestinal obstruction. These patients had previously undergone a total of 43 laparotomies, on average 13 years before. Thirteen patients had undergone one previous laparotomy, five had two previous laparotomies, four had three, and two had four. One patient had no previous history of surgery.

Laparoscopic treatment was possible in nine patients including three with bands and six with more generalized adhesions. In 16 patients, laparoscopy had to be converted to open laparotomy, 13 immediately and three secondarily. Immediate failure was due to the impossibility of finding and/or treating the cause in seven cases, intestinal injury in four cases, intestinal necrosis which required resection in one, and missed right colonic carcinoma in one. The causes of secondary failure were incomplete liberation of the adhesions (one case), recurrent volvulus (one), and missed left colonic carcinoma (one). The mean hospital stay and the duration of postoperative ileus were both significantly shorter in the laparoscopy group than in the laparoscopy plus laparotomy group ($P < 0·001$). Two complications, with one death, occurred in the laparoscopy plus laparotomy group.

In conclusion, laparoscopic treatment of intestinal obstruction is possible but in fewer than half of cases. Failures are related to the difficulty with which the abdomen may be explored. Laparoscopic treatment should not be pursued if difficulties arise. Its role in the prevention of recurrence is not yet possible to assess.

Laparoscopic abdominoperineal resection of the rectum: assessment of adequacy of excision

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In laparoscopic abdominoperineal resection of the rectum (Lap-APR) an abdominal incision is completely avoided as the tumour is delivered through the perineal incision. The view provided in the pelvis by laparoscopy is significantly better than at laparotomy and allows excellent anatomical definition and meticulous dissection. In the present study, adequacy of excision was compared in patients undergoing Lap-APR ($n = 7$) with those undergoing open abdominoperineal resection (Op-APR) ($n = 16$). In all patients the procedure followed malignant disease; Duke's staging and Jass score were similar in both groups. The tumour was not macroscopically fixed in any patient.

	Lap-APR ($n = 7$)	Op-APR ($n = 16$)
Radial margin (cm)	0·5 (0·1–1·5)	0·9 (0·1–3·6)*
Radial margin involved (no. of patients)	0	2*
Median (range) no. of nodes	9·5 (6–14)	6 (1–14)*

**P* not significant (Mann–Whitney *U* test)

Nodal harvest and the extent of radial excision were similar in both groups. However, two patients in the open group had microscopic radial margin involvement although they were macroscopically clear at surgery. Although long-term follow-up is required to monitor local cancer recurrence, laparoscopic rectal dissection appears as effective as open surgery and may allow a more precise assessment of excision margins.

Laparoscopic cholecystectomy under epidural anaesthesia: an ideal combination of minimally invasive surgery and minimally invasive anaesthesia

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Epidural anaesthesia has been reported to have beneficial effects in surgical procedures. In the present study the outcome of using epidural anaesthesia in patients undergoing laparoscopic cholecystectomy was evaluated. A total of 61 unselected patients (39 women, 22 men), mean age 46·9 (range 20–86) years, mean weight 71·7 (range 46–125) kg with symptomatic gallstone disease underwent laparoscopic cholecystectomy under epidural anaesthesia. Ventilatory measurements and arterial blood gas analyses were performed before operation in the horizontal supine position with analgesia applied at the T5–T10 level, after intra-abdominal insufflation of carbon dioxide for pneumoperitoneum and at the end of the procedure. During the procedure patients were maintained with an oxygen insufflation of 3 litres per min through an anaesthetic face mask. Intraoperative sedation was given if necessary. No significant changes in minute ventilation or arterial blood gas measurements were observed. Furthermore, no intraoperative or postoperative anaesthetic or surgical complications occurred. Our experience demonstrates that epidural anaesthesia is safe to use in conjunction with laparoscopic cholecystectomy and is an acceptable anaesthetic technique even for unselected patients.

Laparoscopic peroperative cholangiography

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Between January 1990 and October 1992, 371 laparoscopic cholecystectomies were performed. From July 1990, 309 patients had attempted peroperative cholangiography (POC). The technique was successful in 277 cases (90 per cent). Of these, 214 patients showed no clinical or biological symptoms of common bile duct (CBD) stones. Seventeen CBD stones (7·9 per cent) were demonstrated by POC. Nine of them were detected by preoperative intravenous cholangiography (IVC) and eight (3·7 per cent) were thus unsuspected. Among the 63 other patients with symptoms of choledocholithiasis, 11 (17 per cent) had a CBD stone shown by POC. Five (7·9 per cent) were not revealed by IVC. In conclusion, POC was successfully attempted in 90 per cent of cases, and allowed detection of 5 per cent of CBD stones unsuspected by preoperative IVC.

How to avoid complications in laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is widely accepted as the treatment of choice for cholecystolithiasis. Between March 1990 and December 1992, 750 laparoscopic cholecystectomies were performed. The conversion rate to open surgery was 2·5 per cent (19 patients). One patient died (0·13 per cent). There were seven (0·9 per cent) major and eight (1·1 per cent) minor complications, which were due to four risks specific to the procedure: blind introduction of the first trocar (one perforation of the colon), main bile duct injury (one), clip migration (one biliary fistula) and injuries produced by electrocauterization (one duodenal perforation, one perforation of the colon). Each of these risks can be avoided by meticulous application of the following rules: use of a Hasson cannula, routine intraoperative cholangiography, ligation of the cystic duct in the presence of inflammation, and avoidance of monopolar coagulation in dissecting Calot's triangle. Conversion to open surgery should usually be undertaken as the result of a difficult or anatomically unclear dissection. Observation of these rules enabled a series of 200 consecutive laparoscopic cholecystectomies to be performed without any major complications.

Laparoscopic cholecystectomy: a prospective evaluation of postoperative comfort, hospital stay and interruption of activity in an 'all-comers' population

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The development of laparoscopic cholecystectomy (LC) in the treatment of gallstones is explained by its theoretical reduction of pain, shorter hospitalization and quicker recovery after surgery. The aim of this prospective study was to evaluate duration of pain, analgesic consumption, hospital stay, and return to work and preoperative physical activities in patients undergoing LC.

Between January and December 1992, 103 patients (84 women, 19 men) with symptomatic gallstones eligible for LC were studied prospectively. Mean age was 52·5 (range 17–88) years. Thirty-six patients (35 per cent) had a professional activity, 33 (32 per cent) were retired and 27 (26 per cent) had a home activity. Conditions of the study were defined before surgery as agreement of the patient: (1) to leave hospital on day 3 after surgery if there are no complications; (2) to ask for analgesics in case of pain; and (3) to remain absent from work for 2 weeks after discharge. Conversions to laparotomy were excluded from the study; LC was successful in 103 of 112 patients (92 per cent). Twenty-six patients (25 per cent) required urgent LC for acute cholecystitis and 77 (75 per cent) underwent elective LC; of these, the laparoscopic procedure was performed after endoscopic sphincterotomy for expected bile duct stones in five cases and after mild acute pancreatitis in six.

There were no postoperative deaths, major complications or reoperations. There were ten minor complications. Mean spontaneous consumption of analgesics was 1·5 g paracetamol on the day of LC, and 0·4, 0·13 and 0·07 g on days 1, 2 and 3 after surgery. Thirty five patients (34 per cent) did not need analgesics during the hospital stay; 68 (66 per cent) requested them from day 1 after surgery. Mean analgesic consumption after LC for acute cholecystitis was 1·9 g paracetamol on the day of surgery, but similar to other patients on other days. The mean hospital stay was 4 days. Thirty-two patients (31 per cent) stayed for more than 3 days (mean 6 days) because of minor complications (ten), asthenia (14) or personal convenience (eight); of these, 16 had acute cholecystitis. There were no rehospitalizations. The mean absence from work was 17 days, but was 20 days in 'professional' patients and 14 days in those 'at home'.

This study confirms that pain is resolved quickly after LC; hence hospital stay may be reduced to 3 days for elective LC, allowing a more rapid return to work than the typical 4-week absence after the open procedure. Moreover, LC may be applied safely to a large majority of patients.

Irrigation and clot removal at laparoscopy

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Advances in laparoscopic surgery have been facilitated by improved instrumentation. High-pressure irrigation devices with hydrodissection capabilities use mechanical pumps or pressurized carbon dioxide. The efficacy of these devices is compared with that of a simple pressure bag with regard to flow rates and time required for fragmentation and removal of a blood clot. A model using 500 g clotted blood and 2 m of small bowel was used to simulate haemoperitoneum. The pressure bag and carbon dioxide devices were connected to a standard vacuum pump (600 mmHg); the mechanical irrigation device had a built-in suction capability (760 mmHg).

Irrigation device	n	Mean clot breaking time (s)	Mean clot suction time (s)	Mean clot clearance time (s)	Irrigation flow rate (ml min^{-1})
Pressure bag	3	10·6	177	188	100
Mechanical	3	7·7	179	186	430
CO_2 pump	3	9·1	177	186	370

The mechanically driven irrigation system had the highest irrigation flow rate. The simple pressure bag connected to a standard vacuum pump was as effective at clot removal as both the mechanically driven suction–irrigation device and the carbon dioxide pump irrigation system connected to a standard vacuum pump. A simple pressure bag connected to a standard vacuum pump is recommended for removing clots. More expensive irrigation devices should be reserved for hydrodissection.

Laparoscopic oöphorectomy: a novel surgical method for ovarian ablation in breast cancer

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Premenopausal patients with breast cancer benefit from ovarian ablation as adjunctive therapy. Laparoscopic oöphorectomy has recently been introduced into this unit as the chosen method of ovarian ablation. Fourteen patients have undergone this procedure within the past year. Thirteen patients underwent the procedure at initial presentation, and one patient presented with a local recurrence 2 years after mastectomy. The mean(s.d.) age of patients was 41·1(3·9) years. All patients had stage I or II disease at presentation; two patients had lobular carcinoma, the remainder ductal carcinoma. A closed laparoscopic technique was employed. The initial cannula was introduced via a subumbilical incision. Two further cannulas were introduced in the right and left iliac fossas. Clips and electrocautery were used and the ovary was removed through the subumbilical incision. Complications were minor. The first patient required conversion to an open procedure and also suffered from a minor wound infection. The remaining procedures were uneventful. Follow-up ranged from 1 to 11 months. Two patients experienced moderately severe menopausal symptoms and the remaining patients experienced minor symptoms. This is a safe and relatively easy procedure to perform. In contrast to pelvic irradiation it provides well defined total ovarian ablation.

An endoscopic view of the surgical anatomy of the inguinal region

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Recent advances in technology have led to a rapid increase in the use of laparoscopy in general surgical procedures. One such recently introduced procedure is laparoscopic hernia repair; potentially, this offers a shorter time to recovery and to return to normal activity, and a significant reduction in groin discomfort for patients. In most laparoscopic procedures, e.g. laparoscopic cholecystectomy and laparoscopic appendicectomy, the anatomy encountered by the surgeon through the laparoscope is essentially the same as that seen in standard procedures. In contrast, laparoscopic repair of an inguinal hernia requires a new interpretation of anatomy and the development of a different technique for repair. The orientation of the anatomy of the inguinal region as seen laparoscopically is unfamiliar to most surgeons. For the procedure to be completed successfully, with neither damage to anatomical structures nor postoperative recurrence, a detailed anatomical knowledge is essential.

In this study, the intra-abdominal anatomy of the inguinal region is described with the aid of diagrams and photographs of dissected post-mortem specimens to aid the surgeon in understanding the anatomy of the region. In addition, the critical elements of repair are discussed with respect to anatomical landmarks.

Laparoscopic hernioplasty with polypropylene prosthesis: a study in 30 patients

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This technique is a useful alternative to avoid the problems of inguinal hernia surgery.

Thirty patients were operated on using this technique from June 1992 to January 1993. The patients chosen were without complicated and/or recurrent groin hernia. Those where general anaesthesia was contra-indicated were not selected. The mean (range) age was 55·4 (22–76) years; all patients were male.

The mean (range) duration of symptoms was 31·1 (1–360) months. The clinical diagnosis was 23 inguinal hernia, three inguinoscrotal hernia and four recurrent hernia. The mean(s.d.) duration of surgery was 64·4(17·1) (range 45–100) min. Intraoperative diagnosis was 23 indirect and seven direct hernias. In all cases a polypropylene prosthesis, attached at Cooper's ligament and inguinal ligament, was placed using staples. In the later patients the prosthesis was covered using a peritoneal flap. Two cases (7 per cent) were converted to open surgery: one for uncontrolled bleeding and the other for undetermined problems.

Postoperative pain was present in 36 per cent of patients; the remainder required no analgesics. Postoperative paralytic ileus lasted a mean(s.d.) of 8·3(5·3) h. Patients were able to walk at a mean(s.d.) of 15·6(8·9) h. Mean(s.d.) hospital stay was 2(1·1) days. Two patients had complications (scrotal haematoma and urinary retention). Although the follow-up is short no recurrences were found. However, while these early results are encouraging, a stringent clinical trial and long-term follow-up is necessary before the role of this new surgical procedure is validated.

Contraindications to laparoscopic cholecystectomy

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A number of relative contraindications to laparoscopic cholecystectomy have been proposed. These include previous operation, morbid obesity, acute cholecystitis and stones in the common bile duct.

A retrospective analysis of 600 laparoscopic cholecystectomies performed by a single surgeon was undertaken to determine whether these relative contraindications led to increased morbidity rates, an increased conversion rate to open procedure or longer operating times.

In all, 128 patients had one or more relative contraindications to laparoscopic cholecystectomy. Morbidity rates were not increased in patients with these risk factors. Acute cholecystitis made the operation longer, but did not increase the conversion rate. It is suggested that attempts at laparoscopic surgery should be made despite these risk factors.

Laparoscopic cholecystectomy: early results and experience

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Laparoscopic cholecystectomy has rapidly become the procedure of choice in our practice for patients with symptomatic gallbladder disease. Since December 1991, 251 cholecystectomies have been undertaken; the patients comprised 25 men and 226 women, ranging in age from 14 to 87 years. The operative technique we employ requires the insertion of three or four cannulas and uses monopolar electrocautery to dissect the gallbladder from the liver bed. The average operating time is 89·5 min. Conversion to an open procedure has been necessary in nine (3·6 per cent) patients. A total of 24 (9·6 per cent) operative complications occurred. There were four cases of bleeding from the site of trocar insertion and six cases of gallbladder rupture. Bile stones were spilled during the procedure in three patients. Bleeding from the blood vessels of Calot's triangle was observed in nine patients. All of these were successfully managed laparoscopically. No common bile duct injury occurred. Most patients who had undergone laparoscopic cholecystectomy were discharged within 48 h of surgery.

We conclude that the procedure is safe and can be performed satisfactorily in most patients with symptomatic gallbladder disease.

Laparoscopic inguinal hernia repair

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Laparoscopic inguinal hernia repair (LIHR) may improve the speed of recovery while maintaining low recurrence rates. Patient-led demand for the operation may not be balanced in the short term by the results of prospective randomized trials of LIHR *versus* conventional open hernia repair. A prospective audit of LIHR may therefore play a major role in both short- and long-term assessment of the safety of the procedure, the quality of life and the recurrence rates after LIHR. Some early results of a prospective audit of laparoscopic transabdominal preperitoneal mesh repair of 37 patients are given.

Median operating time was 55 min and median cost of consumables £48. Median (range) diameter of direct defects was 3 (1·5–4·5) cm and of indirect defects 2 (1–4) cm. Complications were minor: three superficial wound infections, three scrotal bruises, and two cord haematomas. In two patients laparoscopic repair was converted to open operation. One recurrence has occurred, suggesting that the mesh used was of inadequate size. The median time to return to normal activity was 4 days and to return to work 12 days.

The results of postoperative visual analogue pain scoring over 3 weeks and the use of analgesia will be presented with comments on operative technique. The present results encourage further close assessment of LIHR.

Laparoscopy of emergency surgical abdominal disease

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Diagnosis of acute surgical diseases (traumatic and inflammatory) is often difficult and errors often occur. Unnecessary laparotomies are performed and surgical intervention is delayed; in both cases operative mortality is higher. Emergency laparoscopy is a valuable diagnostic method and may even be useful in patients with postoperative complications.

This report analysed results of 541 laparoscopies (324 emergency cases). Most emergency laparoscopies were for cases with acute cholecystitis ($n = 89$), abdominal trauma ($n = 48$), perforated ulcer ($n = 40$), acute pancreatitis ($n = 30$), and early postoperative complications ($n = 17$). The risks and complications of laparoscopy in this series were insignificant.

With the help of laparoscopy, an accurate diagnosis can be made, the proper method of treatment planned and the appropriate approach to the abdomen decided.

Complications of laparoscopic cholecystectomy

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Between August 1991 and January 1993, 600 laparoscopic cholecystectomies (LCs) were performed. Of the 600 patients undergoing LC, 474 (79 per cent) were female and 126 (21 per cent) were male. Mean age of the patients was 51 (range 19–80) years. Seventeen laparoscopies (2·8 per cent) were converted to laparotomy because of technical difficulties. The mean operating time was 43 (range 15–120) min. There was no mortality or extrabiliary morbidity. There were four cases (0·6 per cent) of biliary morbidity (bile duct injury). Peritonitis caused by bile leakage was found in two cases. The postoperative hospital stay was 2–7 days; 62 per cent left on the first or second day after operation.

It is concluded that LC can be safely performed with low morbidity, and offers shorter hospitalization and postoperative recovery.

Laparoscopic repair of inguinofemoral hernia recurrence

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The application of a preperitoneal non-reabsorbable mesh (Rives–Stoppa method) has proved to be a valid approach to the treatment of inguinofemoral hernia recurrence. Basically the same operation, performed laparoscopically, is described. A total of 21 patients (14 men, seven women; age range 36–71 years) underwent 'open' laparoscopy under general anaesthesia. To identify the hernia defect, the peritoneum was incised from the top of Hasselbach's triangle to a point lateral and superior to the internal inguinal ring. Two peritoneal flaps were created, the hernia sac pulled into the abdomen and the entire inguinofemoral region was well exposed and then covered by a mesh of 76·2 × 127 mm which was stapled to the inguinal wall by clips. Lastly the peritoneal flaps were approximated and stapled.

The average operating time was 80 min. The postoperative pain and early complication rate were insignificant. All patients left hospital on the second day after operation and there were no further recurrences.

Although the present results are encouraging, to date the laparoscopic method for hernia repair has not been proved superior to open surgery in the long term. The postoperative benefit to patients is so far the most persuasive argument in its support.

Laparoscopic cystic artery haemodynamics

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Laparoscopic cholecystectomy (LC) is now the preferred method for treatment of cholelithiasis. However, dissection in the area of Calot's triangle can be difficult in the presence of adhesions and inflammation, making exposure of the cystic artery and duct hazardous. A laparoscopic Doppler probe (LDP) has been developed for the identification of the cystic artery in an attempt to facilitate safe dissection. In a consecutive series of 20 patients undergoing LC the LDP was used to detect the cystic artery and the resulting Doppler waveform was analysed on computerized software and the end diastolic ratio (EDR) determined. The gallbladder was graded histologically according to the degree of inflammation (0–6). The EDR is a measure of resistance to flow within the artery. The LDP successfully identified the cystic artery in 100 per cent of cases. Median EDR was 0·47 (range 0·32–0·72). The EDR correlated with the degree of inflammation ($r = 0·86$). In conclusion, the addition of a LDP during surgery improves the safety of dissection and predicts the degree of inflammatory response in the gallbladder wall.

Liver

Effects of allopurinol and *Ginkgo biloba* extract on hepatic ischaemia and reperfusion injury in dogs

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The effect of allopurinol and *Ginkgo biloba* extract on hepatic injury after a period of ischaemia was investigated in dogs. Total ischaemia of the liver was induced in dogs for 1 h while haemodynamic stability was maintained by venovenous bypass. One group of animals ($n = 6$) received allopurinol (50 mg per kg body-weight daily, given orally for 2 days before operation). Control dogs ($n = 6$) were given a corresponding volume of solution, while a third group ($n = 6$) was given *Ginkgo biloba* extract (100 mg per kg body-weight intravenously) 1 h before induction of liver ischaemia. Hepatic enzymes were measured 0, 2 and 7 days after operation. Hepatic biopsies were performed at the time of initial laparotomy before induction of ischaemia and 2 and 7 days after operation. More cellular damage was observed on biopsy specimens obtained from the control group and increases in enzyme levels were also more marked during the 5 days after operation. Enzymatic studies and histopathological changes revealed that allopurinol and *Ginkgo biloba* extract were both effective in protecting hepatic cells against the damage caused by warm ischaemia.

Liver ischaemia and reperfusion in the rat: role of chloroquine, a phospholipase inhibitor, in postischaemic liver blood flow

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Breakdown of phospholipids in the membrane unit of the ischaemic cell may play an important role in the pathogenesis of ischaemia and reperfusion injury. Phospholipases, activated during ischaemia through a calcium–calmodulin mechanism, may be involved in this process of membrane damage.

Choloroquine, a phospholipase antagonist, is used to study the role of this enzyme in the pathogenesis of ischaemia and reperfusion liver injury. The experimental procedure consists of the temporary interruption of blood flow to the left lateral and medial lobes of the rat liver and subsequent reperfusion after a period of ischaemia, recording the postischaemic liver blood flow with a He–Ne laser Doppler flowmeter as an indicator of ischaemia–reperfusion liver injury. The experimental group was pretreated with chloroquine for 5 days before ischaemia. In this group, the recovery of liver blood flow after ischaemia was better than in the untreated controls ($P < 0·001$).

These results suggest a role for phospholipases in the pathogenesis of liver ischaemia and reperfusion injury.

Protective effect of University of Wisconsin–Belzer solution against lipid peroxidation of membranes during simulated oxidative stress following liver ischaemia in rats

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Reoxygenation of the ischaemic liver is accompanied by pathological biochemical processes which are mainly ascribed to the generation and effects of toxic oxygen radicals. These radicals peroxidize membrane lipids and thus damage the integrity of the cell membranes. The most commonly used preservative solution, University of Wisconsin (UW)–Belzer, is designed to limit the generation and effect of these radicals by a combination of allopurinol and glutathione. The protective effect of UW–Belzer compared with Ringer's solution on the lipid peroxidation of the membranes under simulated oxidative stress conditions after different periods of ischaemia was determined.

A total of 72 liver explants of male Lewis rats were stored at 4°C following perfusion with UW–Belzer or Ringer's solution. The liver samples were homogenized in phosphate buffer solution for 1 min and thus saturated with atmospheric oxygen after perfusion (0 h, 3 h, 6 h, 12 h, 24 h and 36 h) and at 3 h, 6 h, 12 h, 24 h and 36 h of cold storage. The membrane lipids were subsequently completely peroxidized by addition of the lipid-soluble radical initiator 2,2'-azo*bis*(2,4-dimethylvaleronitrile). A product of lipid peroxidation, malondialdehyde (MDA), was measured immediately after homogenization and after completion of lipid peroxidation. The difference (δMDA) was then calculated.

The difference in MDA values is a measure of unperoxidized membrane lipids. High δMDA values correspond to a lower lipid peroxidation after reoxygenation.

	Mean(s.d.) δMDA (μmol per g protein)					
	0 h	3 h	6 h	12 h	24 h	36 h
Ringer's	0·72(0·18)	0·57(0·10)	0·63(0·16)	0·52(0·16)	0·61(0·18)	0·19(0·15)
UW–Belzer	2·16(0·61)	2·00(0·22)	1·94(0·21)	1·37(0·40)	1·22(0·53)	0·33(0·24)
*P**	<0·05	<0·01	<0·01	<0·01	<0·05	n.s.

* Mann–Whitney *U* test; n.s., not significant

The results show UW–Belzer solution to have a distinct protective effect against lipid peroxidation up to 6 h after preservation. This effect decreases with time; after 36 h there is no significant difference compared with preservation with Ringer's solution.

It is concluded that the protective effect of UW–Belzer solution against lipid peroxidation is sufficient to prevent membrane damage by toxic oxygen radicals for a period of up to 6 h only.

Hepatic transplantation following total hepatectomy and Whipple's operation for fibrolamellar hepatocarcinoma

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A case of fibrolamellar hepatocarcinoma treated with total hepatectomy, duodenopancreatectomy and split liver transplantation is presented.

A 22-year-old woman was diagnosed as having fibrolamellar hepatocarcinoma involving both lobes of the liver. She was accepted as a candidate for hepatic transplantation after extratumoral dissemination was dismissed. After 2 months on the waiting list and taking advantage of an urgent retransplantation for a child, it was decided to split the donor liver using the right lobe for this patient.

An exploratory laparotomy confirmed massive invasion of the hepatic parenchyma and the irresectability of the tumour. Involvement of hilar and hepatic lymph nodes was found. A radical operation including total hepatectomy, cephalic duodenopancreatectomy and lymphadenectomy of the coeliac axis, hepatic artery and superior mesenteric artery was performed. Subsequently, implantation of the right hepatic lobe and reconstruction of digestive continuity with anastomosis of the pancreas, biliary tree and stomach to a jejunal loop were performed.

In the postoperative period the patient presented with a biliary leak owing to partial necrosis of the extrahepatic biliary tree that required surgical treatment with repair of the bilioenteric anastomosis. The patient was discharged 2·5 months after transplant, and at present she has normal function of the graft and a low-flow biliary leak.

Role of PIVKA-II/DCP and other tumour markers in the diagnosis of hepatocellular carcinoma

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Screening programmes for hepatocellular carcinoma (HCC) are based on repeated ultrasonography (US) and evaluations of α_1-fetoprotein (AFP),

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but many tumours are still missed in the early stages; efforts are made to improve the detection rate of HCC and thus its resectability.

Over a 2-year period, 211 patients were tested for AFP, serum ferritin (SF), tissue polypeptide antigen (TPA), carcinoembryonic antigen (CEA) and des-γ-carboxy prothrombin (DCP or PIVKA-II). Of these, 103 (48·8 per cent) had HCC (of these 79 had cirrhosis) and the remaining 108 (51·2 per cent) had liver cirrhosis (30 patients), liver metastases (20), benign liver lesions (26), non-HCC tumours (18) or other miscellaneous diseases (14). Effectiveness tests were assessed for each marker and cross-tabulated with clinical data to evaluate differences between groups.

AFP and DCP levels were higher in the HCC group (P < 0·05). TPA, CEA and SF were not helpful in discriminating HCC. The combined use of AFP and DCP improved the sensitivity by almost 20 per cent.

	Level	Sensitivity*	Specificity*	Negative predictive value*	Accuracy*
AFP (ng dl^{-1})	20	53·5	98·1	66·5	74·5
CEA (ng dl^{-1})	7	24·4	74·4	48·3	48·8
SF (ng dl^{-1})	140	64·2	64·1	62·7	63·3
TPA (units l^{-1})	95	69·7	65·7	68·2	66·6
DCP (units l^{-1})	0·09	54·4	88·0	63·9	69·3
AFP and/or DCP	–	84·3	77·0	68·9	78·0

*Values are percentages

Nineteen patients with HCC (18·4 per cent) were AFP+/DCP- and 21 (20·4 per cent) AFP-/DCP+: in these cases DCP was of more value in patients without cirrhosis and in Child A patients with cirrhosis when compared with AFP (P < 0·05). The DCP sensitivity rate diminished with worsening liver function (P < 0·05).

DCP is as accurate as AFP as a tumour marker of HCC, especially for patients with preserved hepatic function still amenable to surgery. The serum positivity for either one of the two markers is the modality of choice in the serological diagnosis of HCC.

Resection of hepatocellular carcinoma complicating cirrhosis: a multicentre study

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Hepatocellular carcinoma (HCC) is a complication of cirrhosis. Resection, whenever possible, is presently the treatment that provides the best results, although outcome is related to tumour stage and the severity of cirrhosis. Doubt still exists concerning the risks of resection for HCC. The choice is between partial or complete resection of the liver for small HCC and the palliative treatment of large tumours by hepatic transplantation.

The purpose of the present retrospective multicentre study by the French Association for Surgical Research is to report the results of resection for HCC with cirrhosis performed between January 1984 and December 1988 in 18 French surgical centres. A total of 153 resections were performed (between one and 49 resections per centre). Most resections were performed for patients with Child's grade A disease (72 per cent). Emergency resections were performed in 7 per cent of patients and partial resection in 95·8 per cent; only six patients underwent hepatic transplantation.

Intraoperative ultrasonography was used in 61 per cent of patients. The operative mortality rate was 20 per cent and postoperative complications occurred in 61 per cent of patients. The 1-, 3- and 5-year overall survival rates were 52·7, 30·1 and 17·9 per cent respectively. The survival rate was significantly related to the number of nodules resected and size of tumour but not to the presence of a capsule surrounding the tumour. From the present data it is not possible to compare resection with other therapeutic methods for HCC in cirrhotic liver.

Experience with 102 hepatic resections: indications, techniques and results

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Experience in the past 4 years with 102 hepatic resections in 100 patients, 31 women and 69 men (mean age 56 years), is presented. Indications for liver resection were: 30 secondary tumours, most of them from colorectal cancer; 49 primary tumours, mainly (44) hepatocellular carcinoma (HCC) in liver cirrhosis; two liver resections for trauma and 21 liver resections because of benign disease.

Liver function assessed before operation was normal in 56 cases. Only the 44 patients with liver cirrhosis graded as A or B, according to the Child–Pugh classification, were considered for resection.

A total of 59 anatomical resections (39 major procedures) and 43 non-anatomical resections, mainly of a cirrhotic liver, were performed. Intraoperative ultrasonography was used to delineate liver tumour with safe margins, avoiding large resections in patients with cirrhosis. Hilar clamping was performed in 41 per cent of cases. Frequently, associated procedures were performed: two portocaval shunts, five colectomies, one gastrectomy, one pancreatectomy and one nephrectomy.

The postoperative morbidity was three haemorrhages, eight biliary leaks, and 13 mild liver failures in patients with liver cirrhosis. Ten (10 per cent) patients died after operation, most of them in the HCC–cirrhosis and Klatskin tumour groups. Mortality rate was 3 per cent for secondary tumours and 0 per cent for benign diseases. This experience suggests that risk factors for liver resection are liver cirrhosis, severe cholestasis and associated major procedures.

Intraoperative ultrasonography and enhanced computed tomography in the detection of hepatic metastases

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Seventy-two patients with primary colorectal cancer underwent intraoperative ultrasonography and iodized oil emulsion-enhanced computed tomography (IOECT) of the liver at the time of colonic resection. All of these patients had subsequent IOECT at 6-monthly intervals. Eight (11 per cent) of these patients had palpable hepatic metastases at operation. Fifteen (21 per cent) had metastases detected by intraoperative ultrasonography; in 12 patients (17 per cent), these were confirmed by the immediate postoperative IOECT scan. In two of the 15, metastases were not present on initial IOECT but appeared on subsequent scans. In one patient, the intraoperative ultrasonography result was unconfirmed after 12 months' follow-up. A further three patients who showed no evidence of hepatic metastases at the time of operation developed metastases after a mean follow-up of 14 months. Intraoperative ultrasonography detected more of the patients with hepatic metastases than did palpation alone (P<0·05, Fisher's exact test). Follow-up IOECT detected more patients with metastases than IOE scanning in the perioperative period (P < 0·01) which in turn detected fewer patients with metastases than did intraoperative ultrasonography.

In conclusion, patients undergoing curative colonic resection for colorectal cancer should have intraoperative hepatic ultrasonographic assessment of the liver followed by delayed IOECT to maximize the detection of those with overt and occult hepatic metastases.

Preoperative prediction of resectable hepatic tumours

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While the safety and efficacy of hepatic resection have been widely reported, accurate preoperative assessment is essential to avoid unnecessary laparotomy. Computed tomography (CT) correctly identifies 70 per cent of individual liver lesions when compared with findings at laparotomy. CT during contrast enhancement of the liver via the portal vein, or computed tomographic portography (CTP), is thought to be superior to conventional CT. This study evaluated preoperative CTP in 60 patients and on a lesion-by-lesion analysis compared CTP with palpation, intraoperative ultrasonography and histology of the resected liver. The majority, 54 of 60 patients (90 per cent), had metastases (47 colorectal, seven non-colorectal).

At laparotomy, four patients (7 per cent) were inoperable because of disseminated peritoneal metastases in one, hilar node involvement in one and irresectable liver disease (which had been predicted by CTP) in two patients. Fifty-six (93 per cent) underwent partial hepatectomy. CTP accurately identified and located all lesions found at histology in 51 of 56 patients (91 per cent). In five patients CTP predicted resectability, but missed a small superficial deposit in two and had a false-positive finding in the other three. On a lesion-by-lesion analysis CTP identified 110 of 116 lesions (95 per cent).

CTP predicted resectability in 58 of 60 patients (97 per cent). CTP had a sensitivity of 96 per cent and a specificity of 93 per cent in lesion identification and localization, and is the procedure of choice in preoperative selection of candidates for partial hepatectomy.

Warm ischaemia–reperfusion of the liver: possible antioxidant activity of δ-bilirubin

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δ-Bilirubin can be isolated from the serum of hepatectomized rats and is a product formed by the binding of bilirubin and albumin; it is capable of stimulating hepatocellular mitosis both *in vivo* and *in vitro*. In the light of this activity, it was named liver growth factor (LGF). It was recently shown in cultured hepatocytes and myocytes from the human ventricle that bilialbumin can perform an important antioxidant function in situations of oxidative stress. This antioxidant capacity appears to be even greater than that exerted by α-tocopherol. The aim of this study was to assess *in vivo* the antioxidant capacity of δ-bilirubin in an oxidative stress situation such as hepatic ischaemia–reperfusion.

The study dealt with 35 Wistar rats, 80–90 g, freely fed. All were subjected to laparotomy under ether anaesthesia with induction of warm ischaemia of 70-min duration in the left and middle lobes by clamping the afferent vascular branches and shunting the circulation via the branches of the right lobes. Thus ischaemia of approximately 70 per cent of the liver mass was achieved. The serum δ-bilirubin concentration was determined by reversed-phase high-performance liquid chromatography with blood sampling 5, 60 and 70 min after induction of ischaemia and 5, 15 and 60 min after reperfusion of the ischaemic lobes. At the same times, biopsy specimens were taken from the hepatic lobes to determine the tissue levels of malondialdehyde (MDA), an indicator of lipid peroxidation, using the thiobarbituric acid (TBA) test.

		Ischaemia			Reperfusion		
	Sham	5 min	60 min	70 min	5 min	15 min	60 min
δ-bilirubin (μg ml^{-1})	0·38	0·68	1·17	1·63	1·35	1·33	2·16
MDA (nmol g^{-1})	27·40	33·81	27·58	9·46	5·25	20·99	25·57

Values are mean(s.d.)

The differences between δ-bilirubin and MDA values were significant at every point ($P < 0{\cdot}01$). The maximum standard deviation was never greater than 19 per cent with respect to the means. Throughout the ischaemic period and after 5 min of reperfusion the δ-bilirubin and MDA levels were inversely related. After 70 min of ischaemia, the bilialbumin levels were four times higher than those observed in sham-operated animals, while the tissue MDA levels were three times lower than those of the sham group. After 15 min of reperfusion and maximum oxidative stress, both levels increased.

δ-Bilirubin can exert a physiologically significant antioxidant action in situations of cellular oxidative stress in the liver.

Evaluation of blood clearance of ^{99m}Tc-HIDA as a test of hepatic function: preliminary results in healthy, cirrhotic and transplanted liver

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This study aimed to evaluate blood clearance of ^{99m}Tc-trimethyl-Br-IDA as a test of hepatic function, and to analyse the differences in levels of ^{99m}Tc-HIDA excretion between patients with normal or a transplanted liver.

A total of 18 patients were studied: six with a T tube in the biliary tree because of choledocholithiasis (controls); six with transplanted livers with normal liver function tests (transaminases, bilirubin, Quick test, bile flow); and six with alcoholic cirrhosis of Child's grade C. After administration of an intravenous bolus of 50 μCi of ^{99m}Tc-HIDA, a blood clearance test was performed in all patients and ^{99m}Tc-HIDA bile concentration during 3 h was determined in controls and those with transplanted liver. The tests on these two groups were performed on day 7 after operation.

The blood clearance of ^{99m}Tc-HIDA showed statistically significant differences between controls and cirrhotic patients ($P < 0{\cdot}001$), but not between controls and those with a transplanted liver. The maximum peak of bile elimination of ^{99m}Tc-HIDA was significantly earlier in controls than in patients with a transplanted liver ($P < 0{\cdot}001$), and 90 min after bolus administration the bile concentration of ^{99m}Tc-HIDA was significantly greater in the latter group than in the controls ($P < 0{\cdot}001$).

Measurements of blood clearance of radiolabel proved a simple, economic and fast test of liver function. Patients with transplanted liver show a delay in ^{99m}Tc-HIDA bile elimination in the first week after transplantation.

Influence of pentoxifylline on the extent of necrosis and lipoperoxidation after partial hepatic ischaemia in the rat

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Ischaemia–reperfusion is an important cause of liver injury in transplantation and major hepatic surgery. The effect of pentoxifylline on post-ischaemic liver injury is evaluated.

Partial ischaemia (70 per cent) was induced in male Wistar rats (250–300 g) by occluding the left branches of the portal vein, hepatic artery and bile duct for 70 min. Three experimental groups were studied: sham operated ($n = 5$), vehicle-treated ($n = 10$) and pentoxifylline-treated (50 mg kg^{-1} intraperitoneally 30 min before reperfusion, $n = 10$). Blood samples were taken before inducing ischaemia and 6 h after reperfusion. A piece of the left hepatic lobe was taken from each animal at 15 min after reperfusion and homogenized for determination of TBA-reacting substances. All rats were sacrificed 24 h after reperfusion by exsanguination. Sections taken from the left lobe were stained with haematoxylin and eosin and examined by light microscopy. A score was used to evaluate necrosis, congestion and inflammatory infiltration in each animal.

A significantly lower increment in mean(s.e.m.) alanine aminotransferase and aspartate aminotransferase 6 and 24 h after reperfusion was observed in the pentoxifylline-treated group compared with vehicle-treated animals (9082(6836) and 5635(3866) *versus* 13 871(3683) and 8717(1234) units). TBA-reacting substances in homogenates of lobes from pentoxifylline-treated rats were also significantly lower (31·15(2·90) *versus* 40·63(12) nmol ml^{-1}). Necrosis in the pentoxifylline-treated group was less extensive (45–50 per cent) than in vehicle-treated rats (80–85 per cent). Neutrophil accumulation was also reduced. It is concluded that pentoxifylline may ameliorate hepatic postischaemic injury.

Intraoperative oxygen saturation measurement of liver tissue in warm ischaemia in partial liver resection

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Little is known of the ischaemic tolerance of the human liver and its effects on the state of the metabolism in liver surgery. In a first series with the new method of direct and invasive tissue oxygen saturation ($P\text{O}_2$) detection, the $P\text{O}_2$ of liver tissue in partial liver resections was measured. The data were compared with clinical parameters and metabolic analyses of the intermediate products of glycolysis.

A mean liver $P\mathrm{o}_2$ of 41 mmHg was measured in healthy patients. The $P\mathrm{o}_2$ was measured before and during clamping of the liver, and in the consecutive reperfusion phase in 14 patients undergoing partial liver resection. Before clamping the ligamentum hepatoduodenale these patients showed no difference compared with healthy individuals. After discontinuation of the blood flow a fast decrease to a $P\mathrm{o}_2$ of a mean of 7 mmHg was seen. After an ischaemic period of 30 min and a reperfusion time of 30 min, the $P\mathrm{o}_2$ returned to preischaemic levels. The results correlated with metabolic measurements and the further clinical follow-up without the onset of liver failure.

Intraoperative $P\mathrm{o}_2$ measurement gives a reliable intraoperative statement on perfusion, function and recovery of the liver after warm ischaemia.

Diagnosis, aetiology and therapy of liver abscess

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A retrospective evaluation of the clinical symptoms, aetiology, diagnostic approach and therapy in 56 patients with liver abscesses (1984–1991; 44 pyogenic, 12 amoebic) was conducted. Main symptoms were fever, right upper quadrant tenderness, hepatomegaly and jaundice. Ultrasonography and computed tomography were used for diagnosis.

Patients with pyogenic liver abscesses are generally older (70–80 years) and there is usually a severe underlying disease. The patients are in a bad general condition. The treatment consists of antibiotic treatment and in most cases additional drainage (mostly percutaneous and rarely surgical). Patients with amoebic liver abscesses are younger (around 30 years) and their general condition is good. Serology is an important diagnostic method and very accurate. The treatment consists of antibiotics alone.

The mean time of hospitalization was 33 days with an in-hospital mortality rate of 14 per cent in patients with pyogenic abscesses and 6·5 days with a mortality rate of zero in amoebic abscesses. In recent years surgical drainage has been more and more abandoned in favour of radiological drainage. Surgery remains important in pyogenic abscesses for the therapy of the underlying disease (biliary, pancreatic, gastric, colonic diseases).

Non-colorectal liver metastases: indications for resection

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Between 1973 and 1992, 145 patients with colorectal liver metastases underwent surgery. In the same period, 43 resections of non-colorectal metastases were performed in 40 patients. A total of 17 patients had symptoms, and in the most cases large tumours up to 18 cm in diameter were present. Primary sites included endocrine tumour (five), sarcoma (eight), melanoma (one) and other carcinoma (26).

Wide anatomical resection was necessary in 14 patients (35 per cent), no patient died during operation and there were two complication-related postoperative deaths. Three patients, one of whom died, with wide anatomical resections had liver insufficiency. The mean survival after resection was 27·8 months; however, 11 (28 per cent) patients are still alive, five for > 5 years after resection of a non-colorectal liver metastasis. The longest surviving patient is still alive 11 years after hemihepatectomy for a leiomyosarcoma.

Resection of non-colorectal liver metastases has to be regarded as palliative, but in individual cases a very satisfying result, with the gain of several years without recurrence or symptoms, can be achieved. Regarding the results of this study, the best indications for resection of non-colorectal metastases are symptomatic metastases and secondaries of endocrine tumours, hypernephromas, melanomas or well differentiated sarcomas.

Temporary partial hepatectomy: a new *in vivo* model for studying liver regeneration

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Changes such as an increase in hepatocyte growth factor levels in the plasma or proto-oncogene expression in the liver can be detected within a few hours after 70 per cent partial hepatectomy. A signal for regeneration is thus present very early, but it is not clear whether these early changes observed are sufficient to produce the DNA synthesis 24 h later. To address this question, male Wistar rats were submitted to 70 per cent functional 'temporary partial hepatectomy' by occluding the vascular pedicle of the anterior lobes and cooling them locally below 12°C. After 3 h, the lobes were perfused and reinserted in the abdominal cavity. After a further 19 h, 50 μCi [^{3}H]thymidine was injected and the liver was removed 2 h later. After such a partial hepatectomy, mean(s.e.m.) DNA synthesis (40 825(6937) d.p.m. per mg DNA, $n = 8$) was significantly higher than in intact rats (3389(131) d.p.m. per mg, $n = 3$; $P < 0{\cdot}01$), sham operated animals who underwent a similar manipulation but without occlusion and cooling (16 657(1678) d.p.m. per mg, $n = 9$; $P < 0{\cdot}01$), or after 40 per cent partial hepatectomy (18 057(2554) d.p.m. per mg, $n = 4$; $P < 0{\cdot}05$). The stimulation of DNA synthesis was significantly lower than that observed after a classical 70 per cent partial hepatectomy performed immediately (147 239(13 095) d.p.m. per mg, $n = 8$; $P < 0{\cdot}001$) or after 3 h local cooling (132 473(29 987) d.p.m. per mg, $n = 5$; $P < 0{\cdot}001$). In conclusion, although significant DNA synthesis is obtained after temporary partial hepatectomy, additional factors seem essential for the full regenerative response to partial hepatectomy to be obtained.

Hepatic transcatheter arterial embolization with Lipiodol, doxorubicin and Gelfoam in hepatocellular carcinoma

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Surgical resection can be potentially curative in hepatocellular carcinoma. However, the resectability rate is low (approximately 20 per cent), survival in non-resected patients poor (mean 6 months) and recurrence after excision frequently encountered in the liver remnant. Therefore, several therapeutic transarterial approaches have been attempted. This study reports an initial experience using iodized oil (Lipiodol), doxorubicin and Gelfoam embolization by a percutaneous endovascular technique.

Between October 1991 and November 1992, 13 patients entered the study (12 men, one woman; mean age 65 (range 36–72) years). All presented with histologically proven hepatocarcinoma in a cirrhotic liver. There were two tumours in the left lobe, five in the right lobe and six bilateral. All were diffuse or presented satellite masses (in two cases satellite masses could be detected by computed tomography (CT) only after Lipiodol injection). According to Okuda's classification four were stage I, six stage II and three stage III. The α-fetoprotein levels were $< 20\,\mathrm{ng\,ml^{-1}}$ in three cases, $20–200\,\mathrm{ng\,ml^{-1}}$ in four and $> 200\,\mathrm{ng\,ml^{-1}}$ in six. Tumour size of the main mass, assessed by CT, ranged between 3 and 10 cm. The hepatic artery of the lobe mainly affected was selectively catheterized. A solution of Lipiodol (18 ml) and doxorubicin (60 mg) in a water-soluble non-ionic contrast medium was injected and the arterial branch then occluded with Gelfoam in the 13 patients. After 7 days, the contralateral liver was embolized in the same way in nine patients. This double procedure has been repeated every 6 months in the follow-up period. One patient has already received three courses of double embolization and two have received two. Mean follow-up is 7 (range 1–15) months. Clinical biochemistry is studied every 3 months and CT at 3, 6 and subsequent 6-monthly intervals.

The procedure caused no mortality and only minimal morbidity; fever and pain in two cases was responsive to conventional therapy. Tumour size has remained constant in five patients and was significantly reduced (by 25–50 per cent) in four. The follow-up of the remainder is limited. The α-fetoprotein levels, when raised, decreased after the procedure in all patients. In one patient a left hepatectomy was performed 1 month after embolization; all tumour tissue was necrotic with no signs of active tumour cells. Two patients died during follow-up. The actuarial survival rate is 80 per cent at 1 year.

In conclusion, liver transcatheter arterial embolization with Lipiodol and doxorubicin is a safe procedure, can be repeated during follow-up, allows identification of satellite masses not detectable with conventional CT, controls tumour growth and can be useful as a prior step to liver resection or transplantation. However, a longer follow-up is needed to determine its influence on survival.

Survival rate after resection for hepatocellular carcinoma in cirrhosis

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A total of 32 patients suffering from hepatocellular carcinoma (HCC) and cirrhosis have been treated (25 men and seven women). Surgical treatment consisted of 17 wedge resections, 11 lobectomies and four exploratory laparotomies. Hepatic resection was performed in 28 patients who presented with the following characteristics: Child's grade A cirrhosis in 16 patients, grade B in ten and C in two; focal lesions in 18 patients, multiple or diffuse lesions in ten; neoplasm diameter less than 5 cm in 14 patients, more than 5 cm in 14, with a range from 2 to 16 cm; capsule present in 18 patients and absent in ten; vessel thrombosis was present in 14 patients and absent in 14. According to the Edmondson classification, 14 patients were at level I and/or II and 14 were at level III and/or IV.

The actuarial 4-year survival rate is: 66·7 per cent for Child's grade A patients, no survival at 3 years for grades B and C; 31·7 per cent for patients with focal lesions and 42·9 per cent for those with multiple lesions; 39·3 per cent for patients with tumour diameter less than 5 cm and 20 per cent for neoplasms more than 5 cm; 64 per cent for capsulated tumours and 19 per cent for non-capsulated; 21·7 per cent in cases with vessel thrombosis and 51·9 per cent in patients without; and 60 per cent for patients with Edmondson I/II and no survival for patients with Edmondson III/IV.

In conclusion, hepatic resection is indicated in the treatment of HCC in patients with cirrhosis only when the cirrhosis is Child's grade A and the lesion is solitary, superficial, small (less than 5 cm) and possibly encapsulated.

Neurosurgery

Interactive image-directed neurosurgery: a report of the first 100 cases in Europe of frameless stereotaxy

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The precision of image-directed neurosurgery has previously been obtained only using frame-based stereotactic systems which require peroperative scanning. These have limited applications to general neurosurgery. This paper describes experience with a new system that avoids the need for a stereotactic frame by registering the patient's head to an accurate three-dimensional reconstruction of two-dimensional scan data. Near-instantaneous reformatting of the scan data allows the constant updating of the position of a pointer to be shown relative to the preoperative image. The surgeon is then able to visualize key intracranial relationships of structure and pathology before and during surgery. This provides: (1) an accurate interactive guidance system that allows the surgeon to plan; and (2) precise access to the pathology and extent of resection, which results in smaller craniotomies, less morbidity and a subsequent reduction in operating time and inpatient stay. The system is described and the authors discuss the indications for its use, which include: accurate localization of small deep-seated intrinsic lesions; precise navigation around the skull base; and trans-sphenoidal, vascular and epilepsy surgery. This system represents a major advance in neurosurgical precision and has applications in other surgical disciplines, particularly spinal, orthopaedic, ear, nose and throat, ophthalmic and plastic surgery.

Regional differences in managing subarachnoid haemorrhage: a 3-year audit

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All 85 patients with subarachnoid haemorrhage admitted to the Neurosurgical Units of Queen's Medical Centre and Newcastle General Hospital between January 1990 and December 1992 have been audited. The purpose was to look at different patterns of referral and presentation. Of particular interest were the World Federation of Neurological Societies (WFNS) grade on admission (and on day of surgery), and the intervals from bleed to admission and from admission to surgery. The total length of stay in each regional unit was audited and the outcome as judged at discharge. The authors have tried to identify areas where the quality of care may be improved in the management of subarachnoid haemorrhage. The patients with good grades, WFNS I or II, still show wide variations in the timing of surgery, possibly reflecting the availability of beds, angiogram facilities, and the number of consultants. Newcastle tended to operate earlier and Nottingham later although the overall outcome was similar. Delayed surgery was associated with a higher rebleed rate in patients with good WFNS grades. Direct comparison of outcome between surgical units can be misleading unless strict criteria for comparison can be agreed. To measure quality of care standards must be established and British neurosurgery has, as a specialty, been slow to set these.

Extreme lateral suboccipital transcondylar approach to the clivus and craniocervical junction

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Access to the anterior rim of the foramen magnum, craniocervical junction, clivus and front of the lower brain stem can be obtained by using an anterior, lateral or posteriolateral approach. The access used should provide good visualization of the pathology and the surrounding anatomical structures with minimal retraction of neural structures. Ideally the skull should be entered and anatomical routes followed in such a way that between the surgeon and the lesion is a short straight line. The preferred approach to this region depends on the exact site of the lesion, the nature of the pathology and the aim of the operation. Of particular importance is the superior extent of the lesion, its relationship to the neuraxis and its position relative to the midline.

Experience is reported of the transcondylar suboccipital approach used in 12 patients to remove lesions related to the anterior rim of the foramen magnum, the lateral clivus, the front of the lower brain stem and for access to the vertebrobasilar circulation. This paper discusses some of the limitations imposed both by the location of the pathology and the nature of the lesion. The need for flexibility and the necessity for combined anterior and transcondylar suboccipital approaches in selected cases are emphasized.

Neuro-otological team approach to surgical management of acoustic neuroma

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A combined neurosurgical and otolaryngological approach to the management of patients with acoustic nerve tumours is advocated, and the results of adopting this policy in the management of a consecutive series of 250 patients with 254 acoustic tumours are presented.

Operation was via the translabyrinthine or suboccipital approach. There was a 2 per cent (five patients) perioperative mortality rate. In 89 per cent of tumour removals (226 procedures) the facial nerve was preserved in continuity, and normal or good facial function was observed in 79 per cent (197 patients). Few patients had useful hearing before operation and attempts at hearing preservation in this series were unsuccessful.

Complications included major brain stem ischaemia in three patients (1 per cent), cerebrospinal fluid fistula in 12 (5 per cent) and troublesome facial dysaesthesia in 17 (7 per cent). Not surprisingly, morbidity rates appeared to be increased among patients with larger tumours.

Some patients complained of an unusual type of postoperative dreamlike state that appeared to be a form of hypnagogic hallucination. Neurophysiological mechanisms that might be responsible for this phenomenon are discussed.

The flexibility of a bidisciplinary surgical approach has proven advantageous, and its adoption is recommended.

Growth characteristics of acoustic neuroma: the fate of capsule fragments remaining after tumour removal

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The case histories of 26 patients in whom a fragment of tumour capsule remained attached to important structures after removal of acoustic nerve tumours were reviewed to define the growth characteristics of tumour rests. All patients were monitored using computed tomography and, in some instances, magnetic resonance imaging (MRI).

Of 12 patients who underwent subtotal tumour removal, eight (aged 27–73 years) had a solitary acoustic schwannoma. One patient died from cerebrovascular disease but the other seven were well at the last review (mean 39 (range 18–60) months). Five of the eight patients had no evidence of regrowth at a mean of 25 (range 8–42) months after surgery. Three patients showed evidence of tumour regrowth at 21, 22 and 69 months after operation.

An additional four patients aged 15–51 (mean 31·5) years had central neurofibromatosis and presented with bilateral acoustic nerve tumours. Two of these four patients exhibited evidence of tumour regrowth at 13 and 54 months. Conversely, two patients showed no evidence of regrowth at 33 and 45 months after operation.

Fragments of tumour capsule were left attached to important structures in 14 other patients, who subsequently underwent MRI enhanced with gadolinium diethylenetriamine penta-acetic acid at a mean of 70 months (range 6 months to 12 years) after operation. In seven of the patients tumour could still be detected, and in four of these the tumour rests appeared to have enlarged.

It appears that acoustic neuromas grow slowly but even tiny tumour remnants may persist for many years. An appropriate management policy is discussed.

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Microsurgical treatment of brain metastases

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The surgical treatment of single or solitary brain metastases was unrewarding until a few years ago. Microsurgical techniques and intraoperative use of ultrasonography have decreased the surgical morbidity and mortality rates. In an earlier series (March 1988 to March 1992) concerning 41 hemispheric metastases treated surgically, the mortality rate was 2·4 per cent and morbidity rate 14·6 per cent.

To assess surgically related prognostic factors, 11 hemispheric metastases (single or solitary) from solid cancer treated during the period from January 1992 to March 1993 have been studied. Specifically, these tumours had to be subcortically located (up to 2 cm from the cortical surface) and small in size (3 cm or less in maximum diameter).

After linear skin incision, single burr hole and circular small craniotomy, the lesions were removed through the crown of the involved gyrus or by an intergyral approach. All metastases were localized using ultrasonography and resected microsurgically (tumorectomy). The mean operative time was <2 h. Only one patient had transient neurological deterioration (campimetric deficit). The Karnofsky performance score was always above 0·80. No deaths occurred. These results are due to microsurgical techniques, intraoperative use of ultrasonography and better case selection. A shorter operative time and a minimal craniotomy could be additional positive prognostic factors for supratentorial, small and superficial metastases.

Alkaline elution in cell culture of human glioma: a simple method to quantify drug-induced DNA lesions

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The alkaline elution method has been used to examine the effect of different chemotherapeutic drugs on DNA in several experimental tumours. To quantify drug-induced DNA lesions in human glioma the alkaline elution method was used to measure mitoxantrone-induced DNA single-strand breaks in cell cultures of human astrocytoma and glioblastoma tumours. Mitoxantrone is an anthracene derivative which could be potentially used for chemotherapy of malignant brain tumours.

Glioblastoma or astrocytoma tumours were cultured from patients who had undergone surgery. No chemotherapy or radiotherapy were given before surgery. The cell cultures were incubated for 1 h with different concentrations of mitoxantrone (0, 0·01, 0·1 and 1·0 μg ml^{-1}) at 37°C. Protein-associated and protein-free DNA strand breaks were measured using the alkaline filter methods.

It was found that the alkaline elution method could be adapted to measure DNA lesions in malignant brain tumours and that mitoxantrone induces DNA strand breaks in a dose-dependent manner in both glioblastoma and astrocytoma cells. Although only a small effect was observed at a mitoxantrone concentration of 0·01 μg ml^{-1}, there was a linear increase of DNA strand break frequency induced by the drug between 0·01 and 1·0 μg ml^{-1}. However, the DNA hourly elution rate indicating the strand break frequency increased significantly at the higher concentrations of 0·1 and 1·0 μg ml^{-1} mitoxantrone.

Mitoxantrone is not in therapeutic use for malignant brain tumours at present. However, these results suggest that it has a potential use in patients if a high tissue concentration can be achieved.

Nutrition

Effect on visceral protein synthesis of enteral diets with different proportions of medium-chain triglycerides in portocaval-shunted rats

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Portocaval shunt in healthy rats induces several metabolic changes similar to chronic liver failure. Patients with chronic hepatic failure show a deficient nutritional status, with changes in protein, lipid and carbohydrate metabolism. The liver protein synthesis is impaired and the main fuel for the liver is derived from lipids (69 per cent *versus* 40 per cent in healthy people).

Medium-chain triglycerides (MCT) have been shown to have a beneficial effect on liver protein synthesis with parenteral nutrition in several clinical situations, and in the experimental portocaval shunt. MCT have been used in diets for liver failure, but the effect on liver protein synthesis has not yet been studied. The aim of this work was to evaluate the effect of varying proportions of MCT and long-chain triglycerides (LCT) on liver and jejunal protein synthesis in a model of end-to-side portocaval shunt.

Four groups of 15 rats were subjected to end-to-side portocaval shunting. After 15 days of feeding with standard diet *ad libitum*, they were fed an enteral diet for 8 days, with different proportions of MCT:LCT. Quantitative intakes of nitrogen, lipids and carbohydrates were the same for all groups, in a weight proportion of 20:30:50 respectively. Four groups were established according to the MCT:LCT proportion: A, 0:100 (control), B, 20:80, C, 50:50, and D, 80:20. Protein synthesis was calculated using the flooding dose method of [^{14}C]leucine, described by Garlick and McNurlan.

The nitrogen and calorie intakes were similar for groups A, B and C and less in group D. The urinary urea excretion was similar in all groups. The protein synthesis in the liver, in K_s terms, was higher in groups B and C. The jejunal protein synthesis was similar in all groups.

In conclusion, the addition of MCT to the enteral diet had a negative effect on the liver protein synthesis.

Postoperative enteral nutrition: experience in 311 patients receiving total enteral nutrition after major upper abdominal surgery

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Enteral feeding via a needle catheter jejunostomy (NCJ) following gastrointestinal surgery is an effective mode of feeding and is less expensive than parenteral nutrition. The positive effects of enteral nutrition on postoperative immune function, decreased translocation from the gut and maintenance of gut structure may improve the clinical outcome in patients undergoing major gastrointestinal surgery.

In a retrospective study, gastrointestinal side-effects related to feeding scheme and type of diet, and catheter-related complication rate, were evaluated in 311 such patients with placement of a NCJ and postoperative enteral nutrition, from 1982 to 1992. Enteral nutrition was started at 3–5 days after surgery in 95 patients, using a peptide-based enteral diet, the rate of gastrointestinal side-effects was 40 per cent and led to discontinuation of enteral nutrition in 24 cases (25 per cent). A group of 100 patients received a non-elemental diet, diarrhoea occurred in 30 per cent of cases and enteral nutrition was discontinued in 12.

The remaining 116 patients received total enteral nutrition with a non-elemental diet starting 12 h after surgery, the nutritional goal of approximately 8400 kJ day^{-1} being reached on day 3 after surgery, diarrhoea was noted in 18 per cent and required cessation of enteral nutrition in nine patients. One catheter dislocation into the abdominal cavity was reported, infection of the catheter entrance at the lateral abdominal wall led to surgical intervention in three cases.

It is proposed that enteral feeding after gastrointestinal surgery should be started within 12 h after operation using catheters placed beyond the pylorus, such as NCJ or percutaneous endoscopic jejunostomy. The use of elemental diets has no indication in the postoperative period. The early use of fibre-supplemented nutrition should be investigated in further studies, but may be superior to other formulae regarding the occurrence of gastrointestinal side-effects.

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Oesophagus

Surgical treatment of nutcracker oesophagus: long-term follow-up

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Nutcracker oesophagus (NO) represents the most common oesophageal motility disorder in patients with non-cardiac chest pain and is found in 27–48 per cent of these patients; it is characterized by normal peristaltic progression with simultaneous contractions <10 per cent and mean distal oesophageal wave pressure >180 mmHg. Changes in motility patterns have been reported in the literature so that at the present time NO diagnosis needs to be confirmed with a second manometric examination performed at least 3 months later. In some instances NO can be manifested by severe incapacitating symptoms refractory to medical therapy. However, surgical treatment is very rare (up to now not more than ten cases have been published in the literature). In the present study long-term follow-up of three cases of NO associated with mid-thoracic oesophageal diverticula treated surgically at this institution between 1988 and 1990 is reported.

All patients (two women, one man, mean age 65·4 years) were evaluated by means of barium meal, endoscopy, manometry, 24-h pH manometry and oesophageal scintigraphy. Mean(s.d.) distal oesophageal wave pressure was 198(15) mmHg. Patients complained of dysphagia and severe chest pain refractory to prolonged medical treatment. Serial electrocardiograms were within normal limits and repeat thallium stress testing showed no evidence of cardiac ischaemia. A repeat motility test confirmed the presence of NO. Patients underwent extended oesophagomyotomy through the left chest, performed from the distal margin of the high-pressure zone at the point where transverse gastric veins are visible up to the aortic arch, carefully preserving the vagus nerve, a modified Belsey IV procedure was also performed. In two patients a stapled diverticulectomy was performed because of the large size of the diverticular pouch.

No major complications occurred in these patients. The mean follow-up was 3·8 years (range 38–51 months). All patients show satisfactory relief of dysphagia and chest pain. Manometric control showed normal peristalsis in the proximal oesophageal body. Along the length of the myotomy absent or low-amplitude peristalsis was recorded.

In conclusion, it is suggested that in a very few selected cases (incapacitating symptoms and associated diseases) long oesophagomyotomy is a useful therapy in the treatment of NO.

Aorto-oesophageal fistula caused by a foreign body

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Aorto-oesophageal fistula is an uncommon and usually lethal condition. There are several causes, such as thoracic aortic aneurysm or carcinoma of the oesophagus. However, little attention has been directed to fistulas caused by a foreign body, with only 89 cases reported in the literature, and just one recorded survivor.

This report details a case of aorto-oesophageal fistula caused by an ingested chicken bone. A 64-year-old man was admitted to the emergency room because of upper gastrointestinal bleeding. He recalled an episode of retrosternal chest pain after eating chicken 8 days before. The site of bleeding could not be visualized by upper gastrointestinal tract endoscopy. The patient suddenly collapsed 2 h later due to hypovolaemic shock. After a second unsuccessful attempt at endoscopy, a Sengstaken–Blakemore balloon was placed and the bleeding arrested. Computed tomography showed free air in the mediastinum. During this exploration, the patient suffered a cardiac arrest and died. Post-mortem examination revealed an oesophageal perforation (caused by the chicken bone) with aortic perforation and a mediastinal fistula.

Suggestions for diagnosis and treatment of this fearsome complication are discussed.

Surgery for oesophageal perforation

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Various therapeutic strategies have been stressed in the treatment of patients with oesophageal perforation but the mortality rate has remained high at approximately 40–60 per cent. Since endoscopic procedures in the diagnosis and treatment of oesophageal stenosis are now widely used, perforation as a complication of these procedures occurs more often. This study investigated whether these patients will also suffer from such high mortality rates. From 1986 to 1993, 14 patients with oesophageal perforation were treated. In eight patients an iatrogenic perforation of a malignant stenosis was detectable during diagnostic ($n = 3$) or therapeutic ($n = 5$) endoscopic procedures. The four patients with oesophageal resection survived, whereas a conservative approach in four patients was lethal in two (one mediastinitis, one bleeding). All six patients with oesophageal perforation (four iatrogenic, two Boerhaave's syndrome) related to benign oesophageal diseases survived. With the exception of one patient with collar oesophageal perforation and conservative treatment all were operated on directly after referral, 1–7 days after perforation. In conclusion, oesophageal perforation with early adequate operative treatment does not carry the reported high mortality rate.

Gastric antral patch oesophagoplasty for benign oesophageal stricture

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Transmural oesophageal stricture because of either reflux or corrosive ingestion is a formidable surgical problem. A new procedure, gastric antral patch oesophagoplasty, provides an alternative to oesophageal resection and replacement for this condition, and has been performed in 16 patients. 15 had reflux-associated strictures and one stricture was due to corrosive ingestion. All had severe irreversible strictures, and most had undergone multiple previous operations.

A full-thickness patch of gastric antral wall, with a blood supply based on the gastroepiploic arcade, was used to widen the strictured segment of oesophagus and was combined with an antireflux procedure where appropriate. Follow-up ranged from 2 to 11 years. Excellent results, with restoration of normal swallowing, were obtained in 12 patients, four patients required further occasional oesophageal dilatation. There were no deaths.

Gastric antral patch oesophagoplasty is a useful alternative to oesophageal resection in patients with irreversible benign oesophageal stricture.

Vigorous achalasia: short *versus* extended myotomy

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Vigorous achalasia has been considered an indication for surgical treatment in which a thoracic approach is recommended for extending Heller's myotomy along the whole of the oesophageal body to the point where the manometric study shows high-amplitude waves. Clinical results and postoperative manometric studies in 16 patients with vigorous achalasia undergoing abdominal surgery with myotomy of the lower oesophageal sphincter (LOS) not extended to the oesophageal body were analysed to assess whether an extended myotomy is necessary in the surgical treatment of this form of achalasia.

The clinical results were excellent to good in all cases. As assessed radiologically, surgery induced a significant decrease ($P < 0{\cdot}01$) in the diameter of the oesophagus. From a manometric viewpoint, the most significant postoperative changes were a decrease in the resting pressure of the LOS and oesophageal body, and notable reductions both in wave amplitude at all levels of the oesophagus and in the percentage of repetitive waves.

These results suggest that vigorous achalasia can be treated surgically in the same way as classical achalasia and question, at least from a therapeutic viewpoint, the use of the term 'vigorous' achalasia.

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Oesophagoplasty for benign oesophageal stricture in children

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A total of 111 children with caustic oesophageal stricture requiring oesophagoplasty are reported. Eighty had a retrosternal colonic transplant: a two-stage oesophagocolostomy in 68 and a one-stage cervical anastomosis in 12. In the retrosternal group there were two cases of total necrosis and three cases of terminal necrosis of the cervical end of the transplant; 12 patients developed anastomotic stenosis at the cervical end of the transplant. The incidence of cervical anastomotic stenosis was 50 per cent (six) in the single-stage group compared with 9 per cent (six) in the two-stage group.

Ten patients underwent a right thoracic retrohilar colonic transplant; seven had redundancy of the graft compared with 9 per cent (seven) in the retrosternal group

Three patients had a jejuno-oesophagoplasty that resulted in total transplant necrosis in two cases and terminal necrosis in one. The remaining 18 patients had segmental resection of the intrathoracic oesophageal stenosis followed by end-to-end anastomosis. The overall mortality rate was 3·6 per cent (four patients). Twenty-six patients were followed for 15 years; 21 had excellent results and five had residual problems. In the authors' experience, although various oesophagoplasty techniques are available with acceptable mortality, the associated morbidity rate remains significant since none of these confers normal oesophageal motility after the substitution procedure. Therefore, every effort should be made to preserve the native oesophagus.

Prophylactic digitalization in thoracic oesophageal surgery

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Cardiac dysrhythmia is associated specifically with thoracic operations, resulting in the prophylactic use of digitalis In a prospective trial of 130 patients, 80 underwent oesophagogastrectomy and 50 total thoracic oesophagectomy (TTO) after random allocation to prophylactic digitalization or not. Digoxin was given by a standardized oral regimen and serum levels adjusted according to serum radioimmunoassay

Screen electrocardiographic monitoring commenced at induction of anaesthesia and continued for 96 h and on alternate days thereafter until discharge. All dysrhythmias were recorded and assessed blind by a cardiologist. In oesophagogastrectomy, only patients with malignant disease suffered dysrhythmia (46 per cent digitalized, 32 per cent not). In TTO the overall incidence was 60 per cent In both groups prophylactic digitalization neither significantly prevented nor controlled dysrhythmia.

It was concluded that prophylactic digitalization is not necessary in surgery for benign disease and does not control or prevent this complication in other groups

Oesophagus: cancer

Oesophagectomy with thoracotomy in thoracic oesophageal carcinoma: 10 years' experience

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Surgical treatment of oesophageal carcinoma remains one of the hardest tasks confronting surgeons, because of the intense care that patients require to reduce morbidity and mortality, as well as the limited success in long-term control of the disease. A complete clinicopathological data record was kept of all patients operated on between April 1983 and November 1992, including a complete follow-up of 90 7 per cent of them. Presented is experience with the operation considered optimal by the authors when the goal of surgery is cure of the disease.

A total of 75 patients (65 male, ten female) were operated on. The operation had a curative intent in 76 per cent of cases and was palliative in 24 per cent (presence of residual tumour at the end of operation). Of oesophagogastric anastomoses, 80 per cent were performed within the thorax and 20 per cent in the neck Locations of the tumours were divided into upper, middle or lower third

Overall hospital mortality rate was 16 per cent (12 patients) In-hospital major morbidity rate (excluding mortality) was also 16 per cent. The causes of both are presented Pathological staging of tumours was as follows (values are percentages). T_{is} 2, T_1 2; T_2 20, T_3 56, T_4 21. In all, 33 per cent of patients had no lymph node metastasis (N_0), while 67 per cent already had nodal metastases (N_1)

Presented are the actuarial survival rates of the patients at 5 years according to the penetration of the tumour in the oesophageal wall and according to the presence or absence of regional or distant lymph node metastases

Results of surgical treatment of Barrett's adenocarcinoma

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From 1984 to 1992, 28 patients with Barrett's adenocarcinoma and four with high-grade dysplasia arising in Barrett's metaplasia were admitted to this department for oesophageal surgery. Surgery consisted of subtotal oesophagectomy in 24, distal oesophagectomy in seven, or bypass operation in one. Operation was carried out with curative intent in 28 patients, four patients underwent palliative surgery owing to non-resectable metastatic lymph nodes in three and a positive margin at postoperative histological examination in one. After operation all patients were discharged home.

Postoperative examination of the resected specimens revealed the presence of neoplastic cells in two of the four patients operated on for high-grade dysplasia. Actuarial survival rate (3- and 5-year) of the 26 patients with adenocarcinoma who underwent potentially curative oesophagectomy was 58 and 41 per cent, respectively Median survival was 16 months for patients with metastatic lymph nodes *versus* 29 months for those with normal lymph nodes, and 22 months for patients with a transparietal tumour *versus* 30 months for those with a non-transparietal tumour. Of the two patients with high-grade dysplasia, only one was alive at 2 years and one died from an unrelated cause at 5 years

Oesophageal resection with extensive lymph node dissection is the treatment of choice for adenocarcinoma arising in Barrett's mucosa High-grade dysplasia present on two successive oesophageal biopsies is an indication for oesophagectomy, as adenocarcinoma is already present in 50 per cent of cases.

Endoscopic palliation of malignant oesophageal stricture with BiCap tumour probe set

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Patients with irresectable malignant oesophageal stricture may benefit from endoscopic palliation One of the methods is bipolar electrocoagulation with the BiCap Tumour Probe This procedure was performed 29 times in 19 patients with irresectable planoepithelial carcinoma and obstructive symptoms The clinical and endoscopic criteria for treatment were. circumferential malignant stricture, oesophageal stricture >5 mm in each direction, no tracheo-oesophageal fistula and life expectancy >30 days.

Treatment was performed endoscopically with local anaesthesia after premedication. In all patients, remission of dysphagia symptoms was observed after 3–5 days. Diminution of dysphagia symptoms lasted 3–8 months BiCap procedures were repeated in some patients when dysphagia recurred. No serious life-threatening complications were observed

It is suggested that this method is a useful approach to endoscopic therapy of oesophageal neoplasms.

Endocrine cells in Barrett's oesophagus: specificity and clinical implications

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Immunohistochemical methods were used to map the number and distribution of endocrine cells and their regulatory peptide products that are implicated in neoplastic transformation in 43 patients undergoing oesophageal resection for benign and malignant disease with and without Barrett's changes. Only 14 per cent of adenocarcinomas contained endocrine cell populations whereas 62 per cent of intestinal and 78 per cent of gastric metaplasias contained specific endocrine cell populations. The intestinal and gastric populations mimicked those expected in normal tissue whereas in 69 per cent of dysplasias the cell populations became aberrant A pattern of endocrine cell differentiation mimicked by that of normal counterpart tissue has not been previously described in Barrett's oesophagus. In addition, the profusion of endocrine cells and the loss of specificity as dysplasia develops have important clinical implications

Surgery for carcinoma of the oesophagus: experience in Latvia

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The incidence of oesophageal carcinoma in Latvia is 3·8 per 100 000 population A total of 105 patients have been treated in the past 20 years. Radical surgery was performed in only 55 cases (52 4 per cent).

For small tumours the operation of choice is transhiatal oesophagectomy with cervical oesophagogastric anastomosis (eight operations), for advanced carcinoma the method of choice is the Lewis operation with high intrathoracic oesophagogastric anastomosis (28 operations). In other cases, the Thorek (16) or Garlock–Sweet thoracoabdominal operation (three) was performed

Leakage at the oesophagogastric anastomosis was observed in 18 cases The postoperative mortality rate was 16 3 per cent

The survival rate at 1, 3 and 5 years was 65·5, 24·7 and 9·4 per cent respectively

Modified three-stage resection for oesophageal carcinoma

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The greater safety and ease of construction of anastomosis in the neck are acknowledged advantages of the McKeown three-stage resection. It is time consuming, however, requiring three separate operations with resultant increased morbidity A modification of this technique has been devised in which right thoracotomy allows early tumour assessment, mobilization and wide dissection followed by synchronous abdominal and neck dissection A 6-year experience with this technique was analysed using Cox's proportional hazards model.

Some 116 patients underwent resection The male female ratio was 1 5:1. There were 75 (65 per cent) squamous cell carcinomas, 37 (32 per cent) adenocarcinomas and four (3 per cent) adenoid cystic tumours There

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was a significant difference between men and women in terms of tumour type and stage, with significantly more women having early-stage squamous tumours ($P < 0{\cdot}05$). Nine patients died in hospital (7 8 per cent). The 1-, 2- and 5-year survival rates were 50, 31 and 26 per cent Factors that had a survival advantage included lower third or cardial site, clear resection margins, node-negative disease and female sex.

We believe that this modification provides acceptable mortality and favourable long-term survival and is the most appropriate procedure for the majority of oesophageal tumours

Chemotherapy, radiotherapy and surgery *versus* surgery alone for oesophageal squamous carcinoma

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Overall survival following resection of oesophageal squamous carcinoma is around 20 per cent at 5 years and in the absence of screening for early cancer is unlikely to be improved by more radical surgery. Multimodal therapy has a potential role but few studies confirm a survival advantage A prospective randomized clinical trial was started in May 1990 in which the results of chemotherapy (cisplatin and 5-fluorouracil), radiotherapy (40 Gy) and surgery (CRS) were compared with those of surgery alone. Of a total of 56 patients recruited to the squamous cell limb, 41 have completed treatment and been followed for more than 3 (mean 10 8, range 3–28) months

	CRS group (n = 20)	Surgery group (n = 21)	P
Patients withdrawn	2	0	n s
Tumours of stage 0–2A (%)	80	38	0 01
Patients with complete regression	6	0	n s
90-day mortality	2	1	n s.
Survival (months)			
Mean	12·2	8 8	n s
1 year (%)	80	50	n s

n.s , Not significant

Some 30 per cent of patients of the CRS group were tumour-free at operation and significant downstaging of the whole group was observed. While a survival advantage is not yet apparent, these findings suggest that CRS may enhance long-term survival The trial continues

Oesophagus: reflux

Gastro-oesophageal reflux after cholecystectomy: a manometric explanation

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Gastro-oesophageal reflux develops in over 30 per cent of patients after cholecystectomy, but lower oesophageal sphincter pressure (LOSP) is not significantly changed. The sphincter function index (SFI) (the product of LOSP and percentage abdominal length), which is a more accurate indicator of cardia competence, was used to assess sphincter function in this study.

Patients were investigated before and 3 months after surgery using 24-h ambulatory pH and stationary manometry. Patients in group 1 ($n = 11$) did not experience reflux after cholecystectomy, patients in group 2 ($n = 13$) had significant reflux after operation, and those in group 3 ($n = 16$) underwent antireflux surgery.

	Mean(s.e.m.) preoperative SFI	Mean(s.e.m.) postoperative SFI	P*
Group 1 ($n = 11$)	903(95)	1223(133)	n.s.
Group 2 ($n = 13$)	718(98)	507(115)	0·018
Group 3 ($n = 16$)	198(29)	1041(171)	0·001

*Wilcoxon signed rank test; n.s., not significant

Group 1 showed no conspicuous change in the SFI after cholecystectomy, while in group 2 the SFI was significantly reduced. This difference was not evident on LOSP measurement alone. Nissen fundoplication produced a competent sphincter in group 3 patients, which was reflected by a significant increase in SFI. Gastro-oesophageal reflux after cholecystectomy is caused by sphincter incompetence, the aetiology of which is unclear. Restoration of competence by antireflux surgery was confirmed in group 3 patients. The SFI is a more accurate measurement of sphincter competence than LOSP alone.

Laparoscopic Nissen fundoplication

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A total of 95 patients (55 men, 40 women) of mean age 47 (range 17–76) years not responding to conservative treatment for gastro-oesophageal reflux disease (GORD) were treated with laparoscopic Nissen fundoplication. Of these, 72 patients presented with heartburn accompanied by oesophagitis grade II or III as diagnosed by endoscopy. In 11 patients heartburn was accompanied by grade I oesophagitis, whereas in 12 patients an atypical pain was accompanied by grade II oesophagitis. In these latter 23 cases, manometry and pHmetry linked the symptoms to GORD. The mean duration of previous medical treatment was 34 (range 6–180) months. The American Society of Anesthesiologists (ASA) operative risks were as follows: 80 grade I, 13 grade II and two grade III. Thirty-five patients had had previous abdominal surgery.

Five cannulas were needed for operation. The lesser omentum and then the phreno-oesophageal ligament were incised with a coagulation hook. The posterior wall of the oesophagus was dissected from right to left until the left crus could be seen. The short gastric vessels were subsequently isolated and clipped, thereby permitting mobilization of the greater curvature. A fundal floppy wrap at least 5-cm long was created and sutured by five separate intracorporeal knots.

There were four peroperative complications: one gastric perforation, two pleural perforations and one liver laceration. There were three conversions to laparotomy: one because of a defective needle holder and two because of left liver lobe hypertrophy. The mean hospital stay was 3·9 (range 2–10) days. Morbidity included one wrap necrosis and two pulmonary complications (hospital stay 10 days). One patient presented an incisional hernia on a trocar site on the linea alba. No recurrent heartburn has been observed in a short follow-up period (mean 227 (range 4–626) days). Mild dysphagia during the first 3 months after operation occurred in 12 patients. There was, however, no long-term dysphagia. There was one case of gas bloat and one case of clip migration into the oesophagus. Endoscopy was performed in 36 patients during the third postoperative month. A normal mucosa was seen in 35 patients, and one patient presented with asymptomatic grade I oesophagitis.

Nissen's fundoplication is feasible by laparoscopy. This technique improves the patient's comfort and shortens the hospital stay. Further evaluation and long-term follow-up are warranted.

Manometric evaluation of the lower oesophageal sphincter in gastro-oesophageal reflux disease: a modern approach

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Gastro-oesophageal reflux disease (GORD) is a multifactorial process, in which a defective lower oesophageal sphincter (LOS) is often implicated. Identification of patients with GORD and a defective LOS is relevant, since these patients show frequent relapses after medical treatment and may benefit from surgery. To improve the accuracy of oesophageal manometry in detecting a defective LOS, a computer-aided system was developed that allowed calculation of new LOS manometric parameters, in addition to pressure, and overall and abdominal lengths.

A total of 158 consecutive patients were evaluated with 24-h pH monitoring of the distal oesophagus and stationary oesophageal manometry. LOS evaluation was performed with four side holes at the same level oriented by 90° angles, withdrawing the probe across the cardia at a slow constant speed ($1\ \mathrm{mm\ s^{-1}}$). Pressure data were acquired at 20 Hz and stored on a computer. LOS resting pressure at the respiratory inversion point (LOSP), LOS overall and abdominal length were measured. The mean LOSP inside the sphincteral curve (mLOSP), the area under the sphincteral curve (LOS-AUC) and the three-dimensional LOS 'vector volume' (LOS-VV) were also calculated. A defective LOS was identified if any of these parameters fell below the fifth percentile of the control group (14 healthy subjects).

On the basis of pH monitoring, 53 patients were diagnosed as having GORD; of the others, 18 had primary oesophageal motor disorders, 30 irritable bowel syndrome and 42 GORD-like dyspepsia, 15 were evaluated after Nissen–Rossetti fundoplication. LOSP and mLOSP values showed excellent correlation ($r = 0{\cdot}88$) and no statistical differences. Patients with GORD showed LOSP, mLOSP, LOS-AUC and LOS-VV values significantly lower than those in the other groups ($P < 0{\cdot}001$). A defective LOS, as evaluated by LOSP, LOS oesophageal length or LOS abdominal length, was found in 43 per cent of the patients with GORD. By using LOS-AUC or LOS-VV, the prevalence increased to 49 per cent and to 57 per cent using any of the above parameters. On the other hand, a LOS defective in LOSP, LOS oesophageal length or LOS abdominal length was detected in 11 per cent of patients without GORD, whereas a LOS defective in LOS-AUC or LOS-VV was seen in only 7 per cent.

To summarize, a defective sphincter is detectable in more than half of patients with pH-monitored proven GORD. Computer-aided evaluation of the LOS improves the sensitivity and accuracy of oesophageal manometry, and should be performed routinely in the evaluation of patients with GORD.

Laparoscopic Nissen fundoplication: rationale for a new approach

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From September 1991 to January 1993, 57 adult patients underwent operation for gastro-oesophageal reflux disease (GORD) with ($n = 33$) or without ($n = 11$) sliding hiatal hernia, paraoesophageal hernia without reflux ($n = 4$) or failure of a previous antireflux operation ($n = 9$). The operation was completed by laparoscopy in 28, laparotomy in 25 or left thoracotomy in four. The major reason for using an open approach was a remedial operation in nine, abdominal wall-related problems in eight, a

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shortened oesophagus in four, and the need for additional surgical procedures in the abdomen in two. Conversion of laparoscopy to open surgery was necessary in two patients owing to hard adhesions in one and liver parenchyma fragility in one. The fundoplication consisted of a subdiaphragmatic Nissen in 46, a supradiaphragmatic Nissen in three, a partial fundoplication in seven, or a duodenal diversion in one. Laparoscopic Nissen fundoplication consisted of a 360°, 2-cm long floppy wrap with division of the short gastric vessels, posterior crural approximation and intraluminal calibration.

Mean postoperative hospital stay was 6·7 days for patients undergoing laparoscopy, 8·6 days for those having laparotomy, and 13·6 days for those having thoracotomy. Of the patients having laparoscopy, 83 per cent resumed their occupational activity within 2 weeks of operation, while all patients but one having laparotomy or thoracotomy returned to work more than 6 weeks after the operation. At follow-up, none of the 57 patients had residual heartburn, and only one had dysphagia. At postoperative barium swallow study there was neither disruption of the wrap nor gastro-oesophageal reflux (GOR). In one patient having laparoscopy, the wrap was found to have partially herniated into the chest. Adequate lower oesophageal sphincter pressure ($\geqslant$6 mmHg) was restored in all patients having laparoscopy who underwent postoperative oesophageal manometry (16 of 16). Postoperative oesophageal acid exposure was normal in 13 of the 14 patients having laparoscopy who underwent 24-h oesophageal pH monitoring.

Laparoscopic fundoplication is effective on GOR. It is as easily feasible as open fundoplication. The factors that are most critical in choosing this approach are an unsuccessful previous antireflux operation, abdominal wall-related problems, a shortened oesophagus, abdominal adhesions and major concomitant surgical procedures. Prompt rehabilitation is the main advantage of laparoscopic over open surgery.

Changes in oesophageal motility following Nissen fundoplication for the cure of gastro-oesophageal reflux

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The authors report their experience on the functional modifications of the high-pressure zone (HPZ) and of the oesophageal body induced by Nissen fundoplication performed for the cure of gastro-oesophageal reflux (GOR). In the past 7 years 80 patients underwent surgery by the open procedure and 12 by the laparoscopic route. Thirty-six patients underwent clinical and instrumental follow-up (manometry, combined 24-h gastro-oesophageal pH monitoring and endoscopy), and the results obtained were compared with those of a control group of 15 healthy individuals. Compared with the control group the patients showed a reduced lower oesophageal sphincter tone before surgery ($P < 0{\cdot}001$) and an increase in mean(s.d.) percentage of hypotonia (28·16(10·54)) ($P < 0{\cdot}01$) and multipeak (18·16(10·54)) ($P < 0{\cdot}05$) waves. All patients were submitted to a calibrated Nissen procedure with intraoperative manometry (mean(s.d.) 28·15(8·23) mmHg for 3·04(0·64) cm). At clinical and instrumental follow-up (mean(s.d.) 43·15(9·21) months) five patients complained of transient symptoms which disappeared in 3 months; one patient showed pyrosis and one had chest pain. The other 30 patients were asymptomatic. Measurement of pH revealed the presence of hypercompetence of the new HPZ in 35 patients while the patient with pyrosis showed GOR relapse because of a disrupted Nissen fundoplication. At endoscopy, first-degree oesophagitis was diagnosed in three patients and the presence of Barrett's ulcer, which was present before surgery in four patients, was confirmed. At manometry the new HPZ resting pressure was higher than the preoperative value ($P < 0{\cdot}001$) and lower than the intraoperative pressure ($P < 0{\cdot}001$), while it showed no difference compared with the control group. The dynamic study revealed a significant reduction of the postdeglutitive relaxation (mean(s.d.) 70(13·5) per cent) compared both with its preoperative value ($P < 0{\cdot}001$) and that of the control group ($P < 0{\cdot}001$). None of the parameters considered for the oesophageal body (percentages of hypotonic, hypertonic, repetitive and simultaneous waves, and wave duration) showed any significant difference compared with the preoperative values. The 19 patients with marked preoperative hypotonic peristalsis showed a certain increase of wave amplitude after surgery (mean(s.d.) 16·63(3·15) *versus* 25·45(5·24) mmHg). The patient with GOR relapse showed a marked hypotonia of the new HPZ.

In conclusion, Nissen fundoplication has proved effective for the cure of GOR. Moreover, it produces a hypercompetence which may be related to incomplete relaxation of the new HPZ. The procedure does not entail significant complications, nor does it inhibit oesophageal motility. In fact, postoperative motor disturbances are similar to those found before operation. Furthermore, an increase of peristaltic amplitude was observed in patients with preoperative hypotonia.

Long-term results of round ligament gastropexy in the treatment of gastro-oesophageal reflux disease

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Surgical indications in the treatment of gastro-oesophageal reflux disease (GORD) must be determined by demonstration of pathology with an early assessment of surgical results to obtain complete and permanent absence of symptoms without any surgical complications or medical treatment.

A prospective study was begun in 1973 of the treatment of GORD and its complications using the round ligament (ligamentum teres) for gastropexy. A total of 119 patients were operated on until 1986. Diagnostic procedures and surgical indications were evaluated and periodical controls were performed including clinical, radiographic, manometric and endoscopic evaluation.

The results obtained in the group of patients over a 5-year follow-up were satisfactory, with 93·3 per cent of results clinically favourable by 'Frenchay Hospital' criteria. A recurrence rate of 6·7 per cent was observed endoscopically. The overall mortality rate was nil and complications were minimal.

Round ligament gastropexy for the treatment of gastro-oesophageal reflux allows a return to normal physiological gastro-oesophageal junction activity. There are no troublesome side-effects of surgery and the symptoms of GORD are cured.

Significance of transmucosal potential difference after surgery for reflux oesophagitis

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Transmucosal potential difference (TPD) represents a reliable index of mucosal integrity. A new technique that allows, under endoscopic vision, evaluation of TPD, pH and the degree of oesophagitis has been reported. The goal of this study was to establish the significance of TPD in the evaluation of surgical treatment of gastro-oesophageal reflux disease (GORD).

Fourteen patients with GORD (eight men, six women, mean(s.d.) age 39·3(3·4) years) were studied. Written informed consent was obtained from each patient. TPD was performed as previously described. Briefly, a pH glass electrode is assembled with a flexible Olympus GIF Q10 endoscope. The tip of the electrode is under direct vision of the endoscopist, ensuring contact with the oesophageal mucosa. A further reference electrode is inserted in a forearm vein to close the electric circuit. The values obtained are recorded with a pH-meter specific for the measurement of TPD. Four degrees of oesophagitis were classified endoscopically. All patients underwent fundoplication, either total (eight) or partial (six).

Before surgery there was a significant relationship between TPD and the degree of oesophagitis evaluated by linear regression analysis ($r = 0{\cdot}741$, $P = 0{\cdot}002$). The mean(s.d.) TPD value of $-0{\cdot}4(1{\cdot}98)$ mV before surgery was significantly different from that of 22·1(3·4) mV after operation ($P < 0{\cdot}001$).

The results suggest that TPD measurement is a safe, reliable and objective test of mucosal damage in patients with GORD. It is of value in the follow-up of such patients after surgical repair.

Anatomy of the cardia and gastro-oesophageal reflux

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It is unfashionable to consider the anatomy of the hiatal region as important in controlling gastro-oesophageal reflux. The anatomy of the cardia has been studied, with particular emphasis on its valvular structure at endoscopy, in 73 patients with and without gastro-oesophageal reflux. A further 25 patients were studied after Nissen fundoplication The yield pressure of the cardia was also measured and the lower oesophageal sphincter (LOS) assessed by conventional manometry and 24-h pH studies

There was a significant correlation between yield pressure and De Meester composite reflux score ($P < 0.05$), but no direct correlation between yield pressure and the pressure and length of the LOS. In an additional series of 49 patients there was no correlation between yield pressure and vector volume analysis of the LOS There was a close correlation between yield pressure and the anatomy of the cardia using two different grading systems ($P < 0.005$) Yield pressure allowed complete separation of successful and unsuccessful fundoplication and the distinction could also be made by endoscopic inspection.

The cardia is a complex structure Its competence in controlling reflux depends as much on its anatomical form as on its function After fundoplication, structural change is more important in controlling reflux than manometric LOS characteristics.

Evaluation of signs of cure after antireflux procedures

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The aim of this study was to find the criteria indicating cure in antireflux mechanism insufficiency after Nissen–Rossetti fundoplication A group of 40 patients (22 men, 18 women) undergoing Nissen–Rossetti fundoplication from 1981 to 1990 was studied. Follow-up ranged from 28 to 170 (mean 92) months The follow-up investigations were anamnesis according to Visick's scale, radiography, endoscopy, 24-h pH-metry, biopsy and isotopic scanning (^{99m}Tc) A total of 31 patients (78 per cent) were symptom-free. There were no abnormalities in endoscopy in 21 patients (52 per cent) and in 23 (58 per cent) 24-h pH-metry results were normal with DeMeester score < 14·75. In isotopic scanning reflux was reported in 29 (72 per cent). Biopsy revealed pathology in 37 patients (92 per cent) 16 had columnar-cell oesophagitis, 13 squamous oesophagitis and eight hyperplasia with abnormal keratosis Taking biopsy into consideration as the basis of cure, after operation microscopic pathology persisted even in those patients without symptoms The results of the diagnostic methods and anamnesis were different. Assessment of the results of endoscopy or isotopic scanning showed high conformity with biopsy (35 of 37, 95 per cent), sensitivity 95 per cent and efficacy 90 per cent, while the results of endoscopy, isotopic scanning or 24-h pH-metry confirmed higher conformity with biopsy (36 of 37, 97 per cent), sensitivity 97 per cent and efficacy 92 per cent

It is concluded that lack of reflux symptoms after the antireflux procedure cannot be the only criterion for cure, biopsy should be performed in all cases to confirm the cure and combining the postoperative results of endoscopy, 24-h pH-metry and isotopic scanning is of equally high value as biopsy in objective estimation of antireflux procedure efficacy

Treatment of reflux-induced oesophageal stricture

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Assessment of the long-term results of 90 patients with reflux-induced oesophageal stricture managed over a period of 16 years is reported. Thirty-seven patients received conservative treatment and 53 underwent surgery

Conservative treatment (drug treatment and dilatation) was indicated in patients who refused surgery and in those who had mild stenosis, were elderly and/or presented with a poor general status

The 53 patients undergoing surgical treatment received preoperative dilatation to determine which operation they were suitable for Nissen fundoplication was performed in cases of dilatable stenosis without oesophageal shortening ($n = 41$). The Collis–Nissen procedure was performed in patients with dilatable stenosis but with major oesophageal shortening ($n = 9$) Three cases with non-dilatable strictures and three with previous surgical failure (two patients from the Nissen and one from the Collis–Nissen groups) had resection of the stricture with colonic interposition ($n = 5$) or resection with gastric interposition ($n = 1$)

There were two postoperative deaths The remaining 88 patients were followed for between 1 and 16 (median 6) years Of the 37 patients receiving conservative treatment, 11 were asymptomatic, 17 required fewer than two dilatations per year and nine needed more than two dilatations per year The results after surgery were considered excellent to good in 34 of 41 patients who underwent Nissen fundoplication, three of nine of the Collis–Nissen group and four of six with oesophageal resection

Pitfalls of laparoscopic Nissen fundoplication

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A total of 54 patients underwent attempted Nissen fundoplication using a laparoscopic technique The procedure was completed laparoscopically in 46 (85 per cent) Eight procedures were converted to open surgery because of difficulty with morbid obesity in two, large hiatal hernia in two, inability to ensure a loose fundoplication in two patients with oesophageal dysmotility, hypertrophied left lobe of liver in one, and inadequate oesophageal mobilization in one patient.

Mean follow-up has been 5 months, ranging up to 15 months. Postoperative complications have occurred in 13 patients. Three of the eight requiring conversion to open surgery suffered pulmonary embolism Five patients have undergone revisional surgery, one for a rolling hiatal hernia, one for recurrent reflux, one for dysphagia associated with oesophageal dysmotility, and two for gastric obstruction because of the inadvertent construction of a fundoplication using the distal body of the stomach.

Postoperative barium meal examination in 28 patients has also revealed that the fundoplication was fashioned using the gastric body rather than fundus in seven, creating a distorted, bilobular stomach Despite this, the five not requiring reoperation all have excellent clinical results

Difficulty may occur during laparoscopic Nissen fundoplication owing to the lack of a three-dimensional image and the altered angle of view, even when using a 30° laparoscope. Full mobilization of the intra-abdominal oesophagus, taking steps to ensure that the correct piece of stomach is utilized for the fundoplication, will lead to reduction of problems

Oncology

Carotid body tumours

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The aim of this study is to present experience in the treatment of carotid body tumours. It is based on four patients presenting with chemodectoma of the carotid body studied over a period of 5 years. There were three women and one man aged 35–64 years. In three patients the lesion presented as an asymptomatic mass of the angle of the jaw and in the fourth was accompanied by headache and dizziness. Diagnosis was suspected by the clinical findings and established by angiographic demonstration of neovascularity, which is pathognomonic of the tumour.

All patients were treated surgically. In three tumour removal was easy and total. In one patient a subadventitial plane was established and the removal was nearly total. This patient's treatment was completed by postoperative radiotherapy. All the patients are alive and well 5, 3, 2 and 1 year after operation.

Role of radioimmunoscintigraphy with labelled monoclonal antibodies in patients with gastrointestinal tumours

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The staging of patients with gastrointestinal tumours is significantly improved by means of radioimmunoscintigraphy, especially using indium-111 labelled B72·3 monoclonal antibody (MAb), which recognizes a tumour-associated mucin-like antigen termed TAG-72. Twenty consecutive patients (16 with active disease and four disease-free) previously operated on for gastrointestinal adenocarcinoma were studied after administration of 3–5 mCi radiolabelled B72·3 MAb. Serum markers carcinoembryonic antigen (CEA) and TAG-72 were raised in seven of 20 patients (CEA, 21·5(13) ng ml^{-1}, TAG 72, 18(4·5) units ml^{-1}). Radioimmunoscintigraphy was positive in 13 patients, detecting 32 lesions, missing only hepatic metastases in two of them. In three patients no uptake was observed at tumour sites, while four disease-free patients were negative. The main clinical outcome of radioimmunoscintigraphy was the detection of unknown clinically silent distant metastases in five cases (two to lung, three to lymph nodes). These tumour sites were later confirmed by other imaging techniques. In conclusion, radioimmunoscintigraphy with B72·3 allowed better staging of patients previously operated on, showing in association with computed tomography (CT) an accuracy of 84 per cent *versus* 75 per cent for CT alone.

Hickman–Broviac or totally implantable systems for systemic chemotherapy

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Long-term venous access for systemic chemotherapy is of paramount importance in the management of patients with cancer. This study reports the results and complications of 93 patients having implantable systems for systemic chemotherapy in this institution. Forty men (43 per cent) and 53 women (57 per cent) of median (range) age 54 (16–76 years) underwent study. All systems were implanted in the superior vena cava via the right subclavian vein. For totally implantable systems, the port was located in a subcutaneous pocket made on the right anterior thoracic wall, and the catheter was pulled through to the puncture site. Group A ($n = 68$) had a fully implantable system, and group B ($n = 23$) had a Hickman–Broviac catheter inserted. The median (range) duration of chemotherapy was 6 (1–71) weeks in group A and 2 (1–13) weeks in group B. The median (range) duration of catheter patency was 139 (4–1003) days in group A and 66 (9–442) days in group B. Complications were observed in 11 (16 per cent) patients in group A and in four (17 per cent) in group B. Five systems (7 per cent) in group A and two (9 per cent) in group B had to be removed.

Prognostic factors and survival in lingual epidermoid carcinoma: analysis of 201 cases

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Carcinoma of the tongue is the most frequent tumour of the oral cavity. A report is presented of 201 patients treated at one university hospital.

A study of survival has been carried out using actuarial analysis in relation to epidemiological, clinical, anatomical, pathological and therapeutic variables. These have been studied through a multifactorial test (Cox's proportional model of risk) of the prognostic factors which affect survival in tongue carcinoma in an independent way. From all epidemiological variables that had an influence on the probability of death a prognosis index (PI) has been defined. Through the PI, a prognostic classification for tongue carcinoma has been established. Patients were classified into four groups according to risk.

On global multifactorial analysis of the 146 patients undergoing operation, the presence of clinical signs (i.e. pain, haemorrhage and external form) which show tumoral dissemination and have an influence on the probability of death were observed. Perineural infiltration and the peritumoral inflammation reaction also have an independent influence on the probability of death.

According to the PI, calculations were made of the survival probability of each patient and it was observed that the higher the PI, the less the survival probability. Therefore, the patients with a PI higher than 63 have shown a survival of 5·41 per cent at 5 years, compared with 93·46 per cent in patients with a PI less than 32.

This study suggests that the classification using PI adjusts the survival in a more homogeneous way than classification in traditional stages.

Modulation of postoperative immune suppression by interleukin 2

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The cytokine interleukin 2 (IL-2) is known to stimulate the proliferation and tumoricidal activity of lymphokine-activated killer (LAK) and natural killer (NK) cells. Surgery (from the induction of anaesthesia) is known to be a potent suppressor of the immune system, including NK and LAK cell cytotoxicity, and this time period coincides with the risk of iatrogenic mechanical dispersal of tumour emboli at operation.

The aim of this study was to modulate NK and LAK cell function in patients with colorectal cancer undergoing curative surgery by the administration of perioperative recombinant interleukin 2 (rIL-2). Patients were randomized to receive rIL-2 or placebo for 3 days before (day −3 to −1) and after (day 0 to +2) operation.

NK and LAK cell activity (expressed as stimulation indices with reference to pretreatment values) was measured on days −3, −1, +1, +7 and +21. NK cell activity enhanced with rIL-2 on days +1 and +7 ($P < 0·05$, Mann–Whitney U test), LAK cell activity enhanced with rIL-2 on days +1, +7 and +21 ($P < 0·05$).

Flow cytometric analyses showed no significant differences in the phenotypic profiles (CD3, CD4, CD16, CD25 and CD56) of peripheral blood lymphocytes. These preliminary results suggest that rIL-2 enhances both NK and LAK cell function in the immediate postoperative period.

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Meningioma *en plaque*: an aggressive approach

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Extensive tumour removal in the region of the anterior skull base requires not only good exposure, but also acceptable reconstruction The objective when treating benign tumours in this region should be a radical resection, with good cosmesis, no visible scars and intact vision A multidisciplinary team is required and there is need for a flexible surgical approach and for a three-dimensional concept with reconstruction of the orbit Three patients with meningioma *en plaque* involving the orbit are presented to illustrate these concepts

Internal hemipelvectomy

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Until recently, tumours involving the pelvis were usually treated by hemipelvectomy with hindquarter amputation A more recent approach to treatment of these tumours is 'conservative hemipelvectomy', which spares the lower extremity.

Three patients (21, 22 and 43 years old) underwent extensive hemipelvectomy for Ewing's sarcoma and chondrosarcoma The femoral head was fixed temporarily to either the remaining parts of the acetabulum or to the iliac wing by a Steinman pin which was removed 6 weeks after operation The patient was treated using traction for 3 months, and weight bearing was gradually allowed after 6 months.

All patients remodelled a neoacetabulum, which gave sufficient stability to the hip joint Walking without external help was possible in two patients and with a cane in the third The latter had also an external sciatic nerve palsy One patient had no limb shortening and the other two had limb shortening of 4 and 5 cm. No local recurrence was observed during a follow-up of 7–48 months

This small experience with internal hemipelvectomy shows encouraging results in terms of tumour control and gait function.

Serum neurone-specific enolase as a prognostic factor in non-small cell lung cancer

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Serum neurone-specific enolase (NSE) levels were evaluated before surgery by enzyme immunoassay in 84 patients undergoing curative surgery for non-small cell lung cancer (NSCLC) The results were compared with similar estimations in 40 healthy subjects and 20 patients with non-malignant pulmonary disease

Mean(s.d.) NSE concentrations were higher in patients with lung cancer (11·7(10·8) ng ml^{-1} (median 9·7 ng ml^{-1})) than in patients with benign disease ($P < 0{\cdot}05$) or healthy controls ($P < 0{\cdot}01$) NSE levels were not related to tumour node metastasis stage nor to histological subtype. At a cut-off level of 15 ng ml^{-1}, NSE had a sensitivity of 27 per cent and a specificity of 96 per cent At this level there was a high likelihood of tumour relapse with a poor 24-month survival rate

These findings suggest that the measurement of NSE would be helpful in the management of patients with NSCLC

Perioperative interferon α administration in patients with advanced malignant tumours: immunological effect and clinical tolerance

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Surgical procedures may be associated with an increased risk of tumour spread secondary to surgical mobilization of the tumour and transient postoperative immunosuppression Recurrence may result either from early growth of micrometastases already present at the time of surgery or from the seeding of malignant cells shed during the operation. Immunomodulators have been proposed to correct the immunological impairment induced by surgical procedures

Between January and July 1992, 23 patients with advanced cancer underwent surgical resection with perioperative interferon α administration Patients received interferon α_{2a} (Roferon-A), by subcutaneous injection daily for 14 days, starting 3 days before surgery Incremental doses were 2, 3, 5, 7, 9 and 12 × 10^6 units for four, four, three, three, three and six patients respectively Peripheral blood lymphocyte subset numbers were assessed using flow cytometric analysis the day before injection (day −3), before surgery (day −1). and on days 4 and 12 after operation. Absolute numbers of total T cells ($CD3^-$) and natural killer (NK) cells ($CD56^+$, $CD3^-$) were determined, as well as auxiliary T cells ($CD4^+$), activated T cells ($CD3^+$, Dr^+), and B cells ($CD19^+$) counts Short-term cytotoxicity of peripheral blood mononuclear cells against K562 and DAUDI target cells in a 4-h standard chromium-release assay was determined.

No World Health Organization grade IV toxicity was observed A significant postoperative fall of the total peripheral blood lymphocyte count, of $CD3^+$, $CD4^+$, $CD19^+$ and $CD3^-56^+$ occurred from day −3 to day 4. The decrease was not significant for $CD3^+$ Dr^+ Values were not significantly different between days −3 and 12, except for $CD3^+$ Dr^+ and $CD3^-$ 56^+ Cytotoxicity against K562 and DAUDI target cells was significantly increased from day −3 to day −1, and from day −1 to day 1, with a significant fall of cytotoxicity against DAUDI from day −3 to day 4

Perioperative interferon α administration is well tolerated even with the 12 × 10^6 unit doses. In spite of treatment and increasing cytotoxic activity, a postoperative fall was observed for the majority of the immunological parameters Further studies are necessary to make comparisons with a control group, to evaluate more patients treated with 12 × 10^6 units daily

Surgery-induced immunosuppression in advanced cancer: immunological parameters during the perioperative period

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The use of immunomodulators has been proposed to correct the immunological impairment induced by surgical procedures, especially in patients with cancer, in whom immunosuppression may favour early metastatic seeding To study further the mechanisms of postoperative immunosuppression, the evolution of various lymphocyte populations following surgery was analysed

Twenty-five patients with advanced cancer underwent surgical resection The mean duration of anaesthesia was 314 (range 90–540) min A total of 14 patients received packed red blood cells (mean 2 units). Peripheral blood lymphocyte subset numbers were assessed the day before surgery (day −1), and at days 4 and 12. Absolute numbers of total T cells ($CD3^+$) and natural killer (NK) cells ($CD56^+$, $CD3^-$) were determined, as well as auxiliary T cell ($CD4^+$), activated T cell ($CD3^+$, Dr^+), B cell ($CD19^+$) and other lymphocyte subsets as $CD3^+$, $CD25^+$, $CD3^+$, $CD8^+$ counts Short-term cytotoxicity of peripheral lymphocytes against K562 and DAUDI target cells was determined.

A significant postoperative fall of the total lymphocyte count occurred from day −1 to 4. The peripheral lymphocyte count subsequently increased and day 12 values were no different than the baseline value. A decrease of both T cell and NK cell populations accounted for the fall of the lymphocytes at day 4 A full recovery of NK cell number was observed at day 12 although T cells were still markedly reduced. $CD4^+$, $CD3^+$, Dr^- and $CD8^+$ lymphocytes decreased in proportion to T cells between days −1 and 4, and $CD4^+$ cells were still markedly reduced at day 12 In contrast, B cells did not undergo significant change during the perioperative period Cytotoxicity against K562 and DAUDI target cells was significantly decreased from days −1 to 4

The clinical significance of these immunological changes in the perioperative period has not been established. However, they provide a rational basis and a means of evaluation for immunotherapy trials in the perioperative period

Pelvic exenteration with low colorectal anastomosis for gynaecological cancer

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Between January 1980 and December 1992, 97 pelvic exenterations were performed (36 anterior and ten atypical, 26 posterior and 25 total). Radiotherapy was performed before exenteration in 69 cases. Thirty-six low colorectal anastomoses were performed among 51 posterior and total exenterations. in 14 of 26 posterior and 22 of 25 total exenterations. Colorectal anastomosis was performed by hand suture in eight patients and by end-to-end stapling in 28. A protective transverse colostomy was fashioned in 22 patients (11 of 22 total exenterations, 11 of 14 posterior). Defunctioning colostomies were closed in only five cases (two of 11 after total and three of 14 after posterior exenteration).

Continence was achieved in 19 of 36 patients: these consisted of 13 of 22 total and six of 14 posterior exenterations with low colorectal anastomosis; nine achieved continence among 12 anastomoses performed without previous radiotherapy or after radiotherapy < 45 Gy, as did ten of 24 with anastomoses performed after previous radiotherapy or concomitant radiochemotherapy ⩾ 45 Gy. Continence was achieved after three of 14 pelvic exenterations performed between 1980 and 1984, five of 17 between 1985 and 1989 and 11 of 20 between 1990 and 1992.

In conclusion, although the type of anastomosis does not appear to be important, a complete lack of tension on the anastomosis seems vital.

Endosonographic staging of advanced gynaecological cancer: results of a prospective study

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Between January 1988 and December 1992, 106 patients with advanced gynaecological cancer were investigated before surgery by gynaecological examination and endosonography under general anaesthesia; abdominopelvic computed tomography (CT) was performed in 91 patients and magnetic resonance imaging (MRI) in 23. There were 61 primary tumours and 45 cases of recurrence. Aetiologies were as follows: 73 cervical cancers (49 primary, 24 recurrent), ten ovarian cancers (five primary, five recurrent), eight endometrial cancers (two primary, six recurrent), five uterine sarcomas (one primary, four recurrent), five vaginal cancers (four primary, one recurrent) and five others. All patients underwent surgery. This prospective study compared data from clinical and imaging examinations to that obtained from histological analysis of surgical resection margins.

According to anterior or posterior tumour extension, the accuracy of clinical evaluation and preoperative imaging were studied for (1) the posterior vesical wall and vesicovaginal septum and (2) the anterior rectal wall and rectovaginal septum. Histological examination revealed vesical involvement in 32 patients and vesicovaginal septum involvement in 35. The accuracy of clinical examination, endosonography, cytoscopy, CT and MRI for vesical extension was 79, 90, 82, 80 and 85 per cent respectively. Cytoscopy was not taken into account for evaluation of extension to the vesicovaginal septum: accuracy was 80, 92, 77 and 75 per cent for clinical examination, endosonography, CT and MRI respectively. Histological examination showed rectal involvement in 23 patients and rectovaginal septum involvement in 30. The accuracy of clinical examination, endosonography, CT and MRI was 93, 97, 89 and 70 per cent respectively for extension to the anterior rectal wall. Concerning the extension to the rectovaginal septum, accuracy was 85, 96, 85 and 60 per cent for clinical examination, endosonography, CT and MRI respectively.

In conclusion, endosonography appears useful in completing examinations for regional extension of advanced gynaecological cancers, with accuracy superior to that of other methods. Since it is performed under general anaesthesia, there is no discomfort for the patient during this low-cost procedure.

Multivisceral operations

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A total of 141 (2·6 per cent) multivisceral operations were performed between 1987 and 1992 from a total of 5423 operations. They do not include radical surgery for lymphatic spread or extended surgery for technical reasons such as splenectomy for injury. These operations were performed for the surgical cure of two or more different diseases, or because of extension or complication of the basic surgical disease. The most frequent multivisceral operations were: resection of colonic cancer adherent to the small bowel and of metastases of the liver, gastrectomy, splenectomy, resection of the pancreas, colon and diaphragm; resection of the liver, gastrectomy, splenectomy and cholecystectomy, and pancreatoduodenectomy and hemicolectomy.

In the group of patients with two or more diseases the extrapolated morbidity rate increased by 8 per cent and the length of hospital stay by 32 per cent. In the group of patients with extended disease the morbidity rate increased by 19 per cent.

Multivisceral resection in treatment of pelvic tumours

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Surgical intervention not only offers a chance of cure, but may add significantly to the quality of life when reconstructive techniques are employed. A total of 39 patients aged 42–79 years underwent multivisceral resection between 1988 and 1993. The initial diagnosis of rectal, urinary bladder and gynaecological tumours (uterus and ovarian) was made in six, 21 and 12 patients respectively. In two patients, radiation enteritis was present. Continent urinary function was achieved by constructing a Kock pouch. In two patients, partial resection of the bladder was followed by plastic repair and re-implantation of the ureters. Low anterior resection was performed whenever possible, to avoid a stoma. There were no operative deaths or serious complications other than in one patient with wound dehiscence.

Risk factors in elective general surgery for malignancy

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Since 1988 all patients undergoing elective surgery have been analysed in a prospective study with the aim of identifying and evaluating risk factors. The risk has been divided into the following groups of factors: the environment, the surgeon, the anaesthesia, the operative intervention, the disease and the patient independent of any current illness.

In 1990, 682 patients (male:female ratio 1·15:1) of mean age 51·6 (range 14–90) years entered the study. Of these, 225 patients (male:female ratio 1·62:1), mean age 59·1 (range 17–90) years, were operated on for malignant disease. Radical resection was performed in 136 cases (60·4 per cent), whereas 89 patients (39·6 per cent) underwent a palliative procedure.

Following operative procedures for malignancy, general complications occurred in 40 cases (17·8 per cent) and local complications were registered in 34 (15·1 per cent), compared with 23 (5·0 per cent) cases of general complications and 39 (8·5 per cent) cases of local complications in surgery for benign disease ($P < 0{\cdot}0001$). A total of five patients died within 30 days following surgery for a malignant disease. Of these, on three occasions the main risk factor was the disease, in one case the surgeon, and in the other, coexisting disease in the patient. There were no deaths in the patients undergoing surgery for benign disease.

Analysing the collected data, the authors could define variables with significant association to general and local operative and postoperative complications after elective surgery for malignancy: sex (male), arrhythmia, pathological electrocardiogram, platelet count $< 150\,\mu l^{-1}$ and duration of operation > 90 min ($P < 0{\cdot}02$).

In this series it is obvious that operative procedures for malignancy have an increased risk of complications and fatal outcome. To consider specific risk factors, radical treatment should be weighed against palliative procedures, especially minimally invasive surgery.

Surgery and brachytherapy in soft tissue sarcoma of the limb

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Soft tissue sarcomas are tumours with a high risk of local recurrence if conservative surgery is performed in tumours larger than 5 cm in diameter. To prevent this problem these tumours are treated using interstitial brachytherapy in association with conservative surgery whenever possible.

Since April 1991, 13 such patients have been treated, with tumour diameters ranging from 10 to 24 cm. Histology of these lesions was. malignant histiosarcoma (four); myxoid liposarcoma (seven), and malignant schwannoma (two).

At the time of conservative surgery, plastic tubes were implanted in the tumour perpendicular to the wound. Seven to 13 tubes were used. Loading was performed 3–5 days later, using radioactive iridium. Brachytherapy dosage ranged from 2000 to 5000 cGy. External beam radiotherapy was used when necessary, to reach the ideal dosage of 5000 or 6000 cGy. Maximum follow-up was 18 months, with ten patients currently alive without disease. Two other patients have shown local recurrence, and were subsequently submitted for another conservative resection. One patient is alive with pulmonary metastases, and no signs of locoregional disease, and the other patient has died, with distant multiple metastases. The two patients that had recurrence locally following primary tumour excision were referred with recurrence after surgery.

Despite limited experience, the authors believe that soft tissue sarcomas larger than 5 cm in diameter are amenable to conservative surgery with an acceptable rate of local recurrence provided adjuvant brachytherapy is part of the treatment.

Detection and *in vivo* grading of soft tissue sarcoma by positron emission tomography

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The purpose of this study was to investigate positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) as a means of visualizing primary and recurrent soft tissue sarcomas. Fourteen patients with various types of soft tissue sarcoma were studied: nine with a primary tumour, five with local recurrence. The tumours ranged from 1·0 to 20·0 cm in size. Four patients had a grade I tumour, four a grade II tumour and six patients had a grade III tumour. An intravenous dose of 370 MBq FDG was administered for PET. In all patients images were obtained, using a Siemens ECAT 951 positron camera. The glucose metabolic rate (MR) was calculated in ten patients. A grade I recurrent liposarcoma 9·5 cm in diameter was not visualized. All other tumours were clearly depicted on PET. Even a 1-cm local recurrence was distinctly visible.

Glucose consumption proved to be higher in poorly differentiated tumours. In grade I tumours the mean(s.d.) MR (μmol per 100 g per min) was 3·8(0·6), in grade II tumours 15·5(8·0) and in grade III tumours 27·8(11·3). The difference in MR between grade I and grade III sarcomas was statistically significant ($P < 0{\cdot}01$). It appears that the sensitivity of PET for detection of soft tissue sarcomas is high (93 per cent). PET may be of value for early detection of local recurrence. Other imaging techniques are often insufficient for this purpose because tissue planes may be distorted by previous surgery and radiotherapy. PET may also be able to provide an indication of the grade of malignancy *in vivo*.

Surgery after radiochemotherapy in treatment of advanced cervical carcinoma

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Between February 1988 and June 1992, 30 patients with advanced epidermoid carcinoma underwent surgery after radiochemotherapy. Initial FIGO stages were: IIIA, two patients, IIIB, four, IV, four, and bulky tumours (> 4 cm) stage IB (four) or IIB (16). Staging was checked under anaesthetic examination with endosonography. Radiochemotherapy was radiotherapy on the whole pelvis delivering 45 Gy over 33 days and chemotherapy on days 1 and 21 which delivered CDDP followed by 5-fluorouracil intravenous continous infusion for 96 h. Brachytherapy (15 Gy) and a parametrial boost (55–60 Gy) were performed after radiochemotherapy. The operations were colpohysterectomy with lymphadenectomy (22 cases), anterior pelvic exenteration (seven) and total pelvic exenteration (one). All but three were performed with curative intent.

No postoperative mortality was observed. The immediate morbidity rate was high: four severe short-term complications (digestive or urodigestive fistula) required a second surgical procedure and seven short-term complications were minor. Two long-term complications required reoperation and ten long-term complications were minor. Histologically complete excision was achieved in 14 cases. Actuarial survival rates at 1, 2 and 3 years were 77, 71 and 63 per cent respectively, with 21, 14 and five patients respectively at risk.

Postoperative morbidity rates can be reduced by the use of a non-irradiated bowel segment to perform urinary diversion after exenteration. Surgery after radiochemotherapy appears to be an important step to obtain local control. Although these results in the treatment of advanced cervical carcinoma are encouraging, prospective studies are needed.

Correlation between histological stage and preoperative levels of CA19.9 and CA195 in colorectal and gastric cancer

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A prospective study was planned measuring preoperative CA19·9 and CA195 levels in serum from patients with gastric and colorectal cancer. Before the surgical procedure, serum values of CA19.9 and CA195 were measured by immunoassay in 100 patients with colorectal and 50 with gastric cancer.

In colorectal cancer, distribution by Dukes' stage was 8, 25, 53 and 14 per cent for stages A to 'D' respectively. Preoperative tumour marker values for stages A to 'D' for CA19.9 were 12·1, 30·5, 65·4 and 200·4 ng ml^{-1} and for CA195 5·8, 10·4, 23·5 and 57·0 ng ml^{-1}. In patients with gastric cancer no statistical correlation was observed with respect to histological stage. Nevertheless, gastric cancer with severe lymphatic spread (more than five positive lymph nodes) or metastasis showed high levels of CA19·9 (275·8 ng ml^{-1}) and CA195 (134·2 ng ml^{-1}) compared with those without metastasis (31·4 and 20·1 ng ml^{-1} respectively). The predictive preoperative value (PPV) for CA19·9 was: A, 23 per cent, B, 37 per cent, C, 79 per cent, and 'D', 92 per cent for colorectal cancer. For gastric cancer without tumour extension the PPV was 34 per cent and with extension 79 per cent. The PPVs of CA195 in colorectal cancer of stages A to 'D' were 27, 36, 69 and 84 per cent. For gastric cancer without extension the PPV of CA195 was 22 per cent and with extension 72 per cent. CA19·9 and CA195 together had PPVs for stages A to 'D' of 31, 41, 84 and 93 per cent. For gastric cancer the combined PPVs for tumour with and without extension were 83 and 36 per cent.

In conclusion, the sensitivity of CA19·9 and CA195 seems to be high in Dukes' stages C and 'D' of colorectal cancer and in advanced gastric cancer. CA19·9 and CA195 together have a higher predictive value than separately.

Oncogenes and clinical outcome in lung cancer

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Fos and *myc* are oncogenes poised at a critical point in the pathways controlling gene expression and neoplastic transformation. Clinical stage of disease is perhaps the most important factor in determining an individual's outcome in lung cancer. Various claims have been made about the prognostic implications of oncoprotein expression. This study compared oncoprotein with clinical stage and expected outcome in 68 patients in each stage of squamous cell carcinoma of the lung. Overall survival rate in stage I disease, excluding patients who died in the perioperative period, was 84 per cent. *Fos* oncoprotein expression in early-stage disease was significantly greater in those who died ($P < 0{\cdot}02$) compared with those who remained alive. *Myc* expression was not significantly different in those who died compared with those who remained alive in either early- or late-stage disease. Overexpression of *fos* is a poor prognostic indicator in squamous carcinoma of the lung.

p53 tumour suppressor in squamous carcinoma, adenocarcinoma and adjacent lung

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Normal p53 acts as a tumour suppressor gene inhibiting other genes involved in neoplastic transformation. Mutations within this tumour suppressor gene lead to a loss of this function which then allows the neoplastic process to transform the cell. The accumulation of the defective p53 protein can be detected in individual cells using immunohistochemical techniques. This study assessed the accumulation of this abnormal product, and hence loss of the tumour suppressor function, in 68 patients undergoing surgical resection for squamous carcinoma and 41 undergoing resection for adenocarcinoma. Immunoreactivity to p53 was detectable in both diseases and in each stage of disease in tumour and peritumour areas but was usually confined to the lobe harbouring the tumour. These results suggest that loss of tumour suppressor function occurs at an earlier stage than has previously been thought in squamous carcinoma, and supports the concept of loss of function at the dysplasia stage before occult tumour development. It provides evidence for mutant p53 oncoprotein accumulation within a significant proportion of early and late stage adenocarcinomas, implicating loss of tumour suppressor function at an early stage of adenocarcinoma development

Clinical significance of oncogenes in malignant melanoma

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Malignant melanoma continues to pose an epidemiological and therapeutic challenge. However, the answers to outstanding questions will only be found with greater understanding of tumour biology. Considerable interest centres on the molecular genetics of cancer and, in particular, the behaviour of oncogenes p53 is the focus of increasing attention because it appears to be expressed in the majority of human cancers, including melanoma

Using flow cytometry, expression of the protein products of two nuclear oncogenes, p53 and *c-myc*, was studied in human melanoma. In addition, the proliferation kinetics of these tumours were measured using bromodeoxyuridine with an *in vivo* technique. These parameters were related to the clinicopathological features of each tumour

Both fresh and fixed material (in ethanol and paraffin-embedded) was investigated in prospective and retrospective studies. Results show both oncogenes to be frequently overexpressed in melanoma, p53 was expressed in 77 per cent of primary lesions and 83 per cent of metastases, while *c-myc* was found in 67 per cent of primary tumours and 88 per cent of secondary tumours. The level of expression of *c-myc* was associated with tumour proliferation and outcome. No such relationship was evident with p53.

Consideration of these markers may lead to improved tumour characterization and an objective platform on which to design future therapy.

Sacral resection and reconstruction with bone cement

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Sacral resection is sometimes the only way to effect palliation of severe pain in patients with tumours involving the sacrum However, many believe the operation to be unacceptable because of the reported operating time, blood loss and complications. A case of retrorectal leiomyosarcoma invading the sacrum with severe pain resistant to combined irradiation and chemotherapy is reported The tumour was removed, with resection of the right two thirds of S2, S3 and S4 The sacrum was reconstructed with bone cement. The operation lasted 3 5 h with a total blood loss of 700 ml. The postoperative course was excellent, with full continence of faeces and urine, complete spinal and pelvic stability, no motor deficiencies and complete relief of the preoperative pain.

In conclusion, complete sacral resection is unnecessary for sacral root pain palliation in unilateral tumour involvement of the sacrum. The sacrum should be reconstructed with bone cement rather than with muscle flaps, to prevent pelvic instability and herniation of the rectum through the sacral defect

Orthopaedics

Morphology of cortical bone revascularization after open tibial fracture and local muscle flap transposition

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Open fractures of the lower limb are difficult to manage even under optimal conditions In addition to severe fragmentation of the bone, there is often avulsion and devascularization of soft tissues, extensive bacterial contamination, and a relatively poor local circulation All of these compromise sound healing. Recently, vascularized muscle grafts have been used to provide soft tissue coverage as well as to encourage early healing of the fracture through an increase in the local blood supply

In an experimental study with 80 New Zealand rabbits divided into four groups the time between the trauma and the soft tissue coverage and successful revascularization was investigated. During anaesthesia all animals had an open tibial fracture stabilized with two screws After 3 or 7 days a local muscle flap was transposed into the defect zone. Histomorphological examinations were conducted at time intervals up to 16 weeks after the transposition.

In the early group, 1 week after the muscle transposition a part of the bone showed necrosis In the next 4 weeks granulation tissue grew with new vessels The vessels then contact with the cortical bone The reintegration is complete after 8 weeks and the granulation tissue changes into a new periosteum In the group with a muscle flap after 1 week, the cortical bone completely necrosed and osteomyelitis resulted

Only an early muscle flap in the first 3 days will successfully revascularize cortical bone in the treatment of open fractures. A late transposition after 1 week will result in necrotic bone and osteomyelitis.

Three-dimensional computed tomography in the preoperative assessment of cementless hip reconstruction

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Experience with multiplanar and three-dimensional computed tomography (CT) in the preoperative assessment of total hip reconstruction is reported and its usefulness compared with that of standard plain radiography. Twenty patients underwent 21 ceramic cementless total hip reconstructions for secondary degenerative arthropathy. In all 20 patients standard transaxial computed tomograms were taken initially. Using advanced software, these were reformatted to give both sagittal and coronal views in 17 patients, in eight of these three-dimensional images were produced. When transaxial images alone were used, further information was obtained in only two of four patients However, when these data were reformatted to give sagittal and coronal views, more accurate details regarding acetabular bone stock were found in 14 of the 17 patients. The use of a complete three-dimensional image gave useful information, additional to that from the multiplanar views, in half of the patients. Overall, the CT images gave additional information concerning femoral head uncovering, acetabular osteophytes, bone stock and orientation in 16 of 21 hips operated on

In conclusion, in routine total hip replacement, even advanced CT is unlikely to offer any advantages over plain radiography In more complex situations, however, this technology is a reliable method of obtaining more detailed preoperative information and its use is recommended in selected patients.

Distal radius fractures in arthroscopic procedures and transarthroscopic operations of the wrist

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Today's conservative or operative treatment of fractures of the distal radius is at best only satisfactory Even with better techniques of osteosynthesis (e g. external fixation) these fractures show unsatisfactory results in 20–30 per cent of cases in the literature and on follow-up Between 1979 and 1984, 956 fractures of the distal radius were treated conservatively The retrospective study of 548 cases by clinical and radiological means showed a severe reduction in function of the wrist and hand in 18 per cent. Another study of 84 operated cases in the years 1989–1990 indicated the same outcome as in the conservatively treated patients This should not be acceptable. Since 1991, in selected cases primary wrist arthroscopy of the fracture of distal radius and/or radiocarpal joint was performed The intra-articular fracture and depression are differentiated With transarthroscopic procedures the articular surface is reduced Subsequent stabilization of the fragments was obtained via percutaneous K wires and/or screws In some cases cancellous bone grafts were inserted percutaneously by distal portals of the radius shaft The management and also the operative procedure and results are presented.

Degenerative spondylarthropathy: treatment by lumbar arthrodesis

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Between 1986 and 1991, 65 patients were operated on for lumbar osteoarthritis There were 33 women and 32 men, with a mean age of 52 (range 30–81) years All patients suffered from posterior lumbar arthropathy with possible degenerative discopathy and interbody osteoarthritis, 14 had lumbar stenosis. Twenty-one patients had grade 3 and 44 grade 1 or 2 disease, according to the classification of the American Society of Anesthesiologists. Symptoms were low back pain with or without sciatica.

Conservative treatment was unsuccessful Before operation clinical, neurological and radiographic investigations were performed At operation via a posterior approach, two plates were fixed with intrapedicular screws according to the Louis' technique. A posterolateral bone graft was performed, and spinous processes removed Laminectomy was carried out if there was lumbar stenosis. Arthrodesis was usually between L3 and S1 depending on the number of diseased vertebrae

Follow-up was 1–6 (median 3) years. One patient died 6 days after operation from a cerebrovascular accident Evaluation of patients was based on clinical assessment according to Cabot's scale, with radiography and electromyography if necessary In all. 59 patients had clinically good results and lumbar arthrodesis was successful in all patients in spite of some broken screws.

Day-case surgery of subcapital and cervical fractures of the femoral neck

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The repair of femoral neck fractures is considered to be major surgery because of the operative procedure, complications and elderly target population (mean age 78 years) Total anaesthesia, the lateral position during operation and sometimes a long period of hospitalization may affect the clinical outcome. Local 'assisted' anaesthesia may allow a short hospitalization and immediate weight-bearing

Thirteen patients have undergone operation in our department between 1989 and 1992, with an average of 22 h of hospitalization and immediate weight-bearing The osteosynthesis by Knowle's pins with a short approach under local assisted anaesthesia and under radioscopic control was used for Garden I and II subcapital and cervical femoral neck fractures.

The results have been encouraging· neither secondary displacement, local or general complications, nor necrosis or non-union have been seen during a follow-up of 18 months. The shortness of the hospitalization period permitted patients rapid recovery

Day-case surgery may have a place in the management of femoral neck fractures.

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Comparison between operative treatment of acromioclavicular dislocation using metal implants and augmentation fixation with Vicryl threads

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Different operative procedures exist for the treatment of ruptured acromioclavicular ligaments. In a retrospective study two different operative procedures were compared, according to their clinical and radiological results. In 36 patients, operative treatment of the ruptured ligament was performed by using Vicryl threads Augmentation of the coracoclavicular ligament was performed in six of these patients, whereas in four the acromioclavicular ligament was repaired Augmentation of both ligaments was performed in the remaining 24 patients using 5 mm Vicryl threads. Postoperative results were documented in 24 patients by clinical examination, ultrasonography and radiology. Dislocation of the acromioclavicular joint of more than 10 mm was found in five patients Using the TAFT score, in five patients an excellent result was achieved, 14 patients had a good result, four patients a satisfying result and one patient a bad result regarding clinical evaluation and ultrasonographic and radiological findings. Compared with 75 patients who were treated by implantation of metal fixators from 1980 to 1985, the same results were achieved by using augmentation with reabsorbable Vicryl In conclusion, operative treatment of acromioclavicular dislocation using Vicryl threads should be preferred, because of the same clinical and radiological results, but without the necessity for a second operative intervention for removal of the osteosynthetic material

Self-reinforced polyglycolide and polylactide rods and screws in the fixation of fractures and osteotomies

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Totally absorbable fracture fixation devices were introduced in the authors' department in 1984 A total of 2100 patients have been managed with these implants, mainly rods and screws made from polyglycolide (80 per cent) or poly-L-lactide (20 per cent). Indications for these implants included fracture of the ankle, radial head and olecranon, chevron osteotomy for hallux valgus, flake fractures in different joints and arthodeses of the ankle, foot and hand regions, as well as epiphyseal fracture in children. Recovery was uneventful in over 90 per cent of patients, the infection rate being 3 per cent The reoperation rate was 2 3 per cent. An inflammatory reaction against the polyglycolide material resulting in spontaneous sinus formation was seen in 2 8 per cent of patients, but not in children.

A 1-year analysis of 102 patients with unimalleolar and bimalleolar fractures treated with rods alone showed good radiographic results in 84 per cent (anatomical ankle mortise) and good functional results in 87 per cent. Fixation of ankle fractures with absorbable polyglycolide or polylactide screws was even more successful. In a study of 145 patients the radiographic and functional results were good in 89 and 98 per cent respectively.

The treatment of fractures of the radial head was highly successful in 20 of 24 cases, eight of whom had a severely comminuted fracture of the radial head before surgery. Fixation of 41 olecranon fractures was successful in all but two cases. There was no difference in success rate whether 3 2-mm rods or screws were used for fixation.

Absorbable rods and screws are now used routinely for fixation of different types of fracture and osteotomy of the cancellous bone in adults, as well as in children. The main advantage of the method is that removal of the implants is not needed, which is important when calculating the operative costs of the surgical unit. The good fixation properties and the low complication rate justify further development and use of absorbable polyglycolide and polylactide implants.

Impingement and the coracoacromial ligament

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Anatomical dissection of 50 shoulders, with measurement and histological analysis of the coracoacromial ligament, was performed The results show that in persons > 50 years of age the coracoacromial ligament does not have a constant form. Three main types were found: quadrangular (48 per cent), Y shaped (42 per cent), and broad band (8 per cent) The Y form and the quadrangular type of ligaments had significantly larger attachments to the coracoid. The broad-band ligament was significantly correlated with height. In 80 per cent of the Y shaped ligaments, those with both medial and lateral bands, the lateral component had the largest attachment to the coracoid. The lack of uniformity of the ligament was emphasized by the absence of statistical correlation between the type of ligament and side, sex, age, midpoint thickness, acromial attachment or the minimum distance between coracoid and acromion.

A previously unreported type of coracoacromial ligament, the multiple-banded ligament, was found, which also had the largest coracoid attachment This multiple-banded version was similar to the Y form but with an additional band extending inferiorly and medially on the coracoid, increasing the likelihood of impingement by this type of coracoacromial ligament. Histological analysis of the ligaments, including the diaphanous section of the Y version, indicates that the multiple-banded type could be more common than this study suggests

Results of femoral fracture treatment

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A prospective study to determine factors affecting mortality, morbidity and postoperative mobility of 1000 patients with femoral neck fracture (525 subcapital, 475 intertrochanteric) admitted to a district general hospital over a 50-month period is described. A total of 25 fractures were treated conservatively with a mortality rate of 60 per cent. The hospital mortality rate of the 975 surgically treated fractures was 11 3 per cent. Discriminant analysis revealed that the best predictor of survival was mobility before injury. The effect of grades 1–6 of mobility before injury on mortality was progressive. The best predictor of operative survival was the mobility score Delay affected the results, but only 30 h after admission, a period in which 75 per cent of patients had undergone operation.

The best predictors of morbidity and discharge mobility were age and mobility before injury Specific attention was given to the results obtained by the 62 surgeons in this series. Experience affected the discharge mobility, but statistical analysis determined its effect to be small.

This study shows that, given a similar distribution of fractures of the femoral neck, surgeons of 1–5 years' experience in orthopaedics and those with greater than 5 years' experience can achieve comparable mortality and morbidity results in hemiarthroplasty and internal fixation.

Treatment of comminuted fracture of the distal end of the radius by ligamentotaxis

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Comminuted fractures of the distal end of the radius with involvement of the joint (C2–3 in the AO classification) are treated by osteosynthesis with Kirschner wires or external fixation. Particularly unstable fractures may be reduced and held by external fixation according to the principle of ligamentotaxis

A total of 73 patients (48 female, 25 male) with C2 (34 patients) and C3 (39) fractures (14 open cases) were treated by external fixation over a period of 4 years. In all, 40 patients (24 female, mean age 69 years, 16 male, mean age 42 years) were followed for a mean of 28 months

All fractures healed. Although the action of the wrist had been restricted for 6 weeks, all patients were able to carry out their usual activities frequently after 3 months In one patient the radius was fractured by a screw during surgery. Significant pin track infection and Sudeck's dystrophy were observed in one patient each.

The mean reduction of dorsiflexion, palmar flexion, abduction and adduction was 10° compared with that in the healthy wrist. Pronation was 3° and supination 12° less than on the unfractured side.

Radiography showed arthrosis of the wrist in three patients. The mean dorsal angulation was 3° (range −5°–15°); the mean angle between the shaft of the radius and the area of the joint was 23° (range 12°–34°). Discontinuity of the articular surface was found in five patients. Most patients with a good radiological result have a good clinical outcome.

Treatment of C2 and C3 fractures of the distal end of the radius by external fixation can be recommended because of the good clinical and radiological results. The technique can be regarded as an alternative to Kirschner wiring.

Factors affecting wear of polyethylene in retrieved total knee replacements

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Over 250 retrieved tibial polyethylene components have been analysed for wear of polyethylene. Duration of implantation varied from 7 months to 19 years. There were 106 unicondylar type prostheses, 85 total condylar replacements, 35 meniscal and 17 stabilized total-knee replacements. All prostheses were assessed for wear by scoring bearing surfaces on a scale of 0 to 5 for delamination, pitting abrasion, deformation, scratching and cement entrapment. Wear scores were correlated with duration of implantation, patients' activity and weight. Crystallinity and oxidation of polyethylene were measured by infra-red microspectroscopy. The tensile strength of polyethylene was determined.

Delamination of polyethylene occurred in some unicondylar designs and in long-term (>10 years) condylar replacement designs. In one design of a meniscal bearing total-knee replacement delamination occurred at the edges of the polyethylene runners due to misalignment of the surfaces resulting from rupture of the anterior cruciate ligament. Abrasion by cement particles occurred predominantly in stabilized and total condylar replacement designs. In all specimens examined crystallinity of the polyethylene decreased under the wear track. There was a significant difference in the ultimate tensile strength of polyethylene from different designs. One of the main factors associated with early delamination in one design was the presence of fusion defects in polyethylene which led to crack initiation and delamination.

Conformity of the articulation *per se* did not appear to be the major factor influencing delamination wear of polyethylene. The quality of polyethylene had a significant effect on wear. Even highly conforming bearing surfaces of the total condylar replacement design type delaminated after long durations (>10 years).

Effect of osteotomy performed by an oscillating saw on bone regeneration

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Bone regeneration may be improved if an Ilizarov osteotomy is performed by a chisel with fragment torsion which causes a spiral fracture. The defects of bone healing after using either a rotatory or an oscillating saw have been reported.

The regeneration of distracted bone was studied in 20 men with bone defects ranging from 4 to 14·5 cm. Five patients underwent osteotomy (after Ilizarov) and in 15 patients the transverse osteotomy was performed by an oscillating saw. In four patients the osteotomy was performed on both main fragments. Bone regeneration was observed in radiographs at regular 4-week intervals. The first signs of ossification appeared after 4 weeks. There were no differences in the bone regeneration between the Ilizarov osteotomy and the transverse osteotomy performed with an oscillating saw. The defects of bone healing after the osteotomy by rotatory or oscillating saw have not been observed in experiments with 30 rabbits.

Transverse osteotomy of long bones with an oscillating saw to produce bone elongation by the Ilizarov method has no effect on the regeneration of distracted bone.

Ionizing radiation and the orthopaedic surgeon

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The orthopaedic surgeon is exposed to increasing levels of ionizing radiation due to the growing number of techniques that use perioperative radiographic imaging. To quantify this potential risk, a prospective survey was conducted to measure radiation levels in a designated trauma theatre.

The study was conducted for 1 calendar month with operative procedures carried out as normal. Measurements were performed using eight standard dosimetry badges, placed at a height of 1·4 m at set points around the theatre. This was designated to record maximum radiation levels given the direction of the primary X-ray beam. In addition, one badge was attached to the operating table and one to the anaesthetic trolley. During the study period 41 cases required X-ray screening, 19 (46 per cent) during internal fixation of femoral neck fractures, a further six cases required the production of nine hard-copy radiographs. Total screening time was 19·7 min, with a mean screening time of 29 (range 8–180) s per case.

At the conclusion of the study all badges were processed at the regional department of medical physics to an accuracy of 10 per cent. The maximum recorded dose was 0·2 mSv at the operating table, all other badges recorded a dose of 0·05 mSv. If these data are extrapolated for a period of 1 year, the maximum dose is in the order of 2·5 mSv, well within the maximum permitted whole-body dose for a member of the public (5·0 mSv per annum).

It is concluded that there is no significant risk associated with current working practice. This is partly due to the use of high-performance image intensifiers with image retention and pulsed fluoroscopy.

Adjuvant local antibiotic therapy: an analysis of 1085 open fractures

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A consecutive series of 1085 compound fractures was treated between May 1983 and July 1992. There were 279 grade I, 364 grade II and 442 grade III open fractures (199 IIIA, 171 IIIB, 72 IIIC). A total of 240 open fractures (group 1) received systemic administration of broad-spectrum antibiotics alone whereas 845 compound fractures were managed with the supplemental local use of aminoglycosides (tobramycin-polymethylmethacrylate beads). All fractures underwent copious wound irrigation, meticulous radical debridement and fracture stabilization.

The overall infection rate in group 1 was 12·1 per cent (29 of 240) and 3·7 per cent (31 of 845) in group 2. The difference is statistically significant ($P < 0.001$). In the grade I category the overall infection rate was 3 per cent (two of 67) in group 1 and 0·5 per cent (one of 212) in group 2. In patients with grade II the overall infection rate was 8 per cent (six of 71) in group 1 and 2·7 per cent (eight of 293) in group 2 whereas the overall infection rate in those with grade III open fractures was 20·6 per cent (21 of 102) in group 1 and 6·5 per cent (22 of 340) in group 2. A statistically significant reduction of the infection rates was evaluated only for the IIIB types for wound infection (group 1 41 per cent (11 of 27), group 2. 6·9 per cent (ten of 144), $P < 0.001$) and for chronic osteomyelitis (group 1. 30 per cent (eight of 27), group 2 6·2 per cent (nine of 144), $p < 0.001$) as well as for the IIIC types for wound infection (group 1 25 per cent (eight of 32), group 2 5 per cent (two of 40), $P < 0.05$).

External fixation in the treatment of multiple fractures

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In the orthopaedic clinic of Kaunas Medical Academy from 1987 to 1993, 18 patients with multiple fractures of long tubular bones were treated using an external fixation apparatus designed especially for such fractures (patent no 1338851). The portable unilateral apparatus contains a screwed bar, rod holders and repositioning devices for each dislocated fragment of bone. Six patients were treated for femur, seven for tibia and two for humerus fractures. Two patients suffered both a femur and a tibia fracture and one had a bilateral femur and unilateral humerus fracture. The apparatus was removed after an average of 5 months. All 18 patients were followed for 1–5 years.

Good results (no complaints, knitting of the bone fragments in good position, full range of motion of the joints) were achieved in 12 patients. Satisfactory results (complaints of mild pain, slight deformation, shortening of the limb by 1–2 cm, limited motion of the joints to up to one-third of normal) were observed in six patients.

Kienbock's disease: prognostic evaluation by magnetic resonance imaging

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The main difficulty in treating stage III Kienbock's disease (Decoulx's classification) is deciding between conservative and non-conservative surgery. This problem would be resolved if the osteogenic potential of bone medulla could be assessed before operation. Plain radiography and scintigraphy do not assess medullary bone potential. Magnetic resonance imaging (MRI) accurately assesses the state of bone medulla and its vascularization (using T2- and T1-weighted acquisitions, performed before and after intravenous injection of contrast) The most valuable technique performed on patients before and after conservative surgery or on non-operated patients appears to be MRI follow-up providing the basis for prognostic staging, which may guide surgical strategy

A prospective study of 25 consecutive patients presenting on plain radiography with stage III Kienbock's disease was conducted. Patients were included if MRI follow-up (two examinations at 6-month intervals) was available. Fifteen patients underwent radial-shortening osteotomy and were examined by MRI before and 1 year after the procedure. Five patients had only postoperative MRI at 3 months and 1 year after surgery Five patients, still non-operated, were examined when diagnosis was made and 6 months later.

MRI was performed using T2- and T1-weighted acquisitions. T1-weighted images were obtained before and after contrast injection A prognostic subclassification of stage III Kienbock's disease was established, depending mainly on the volume of the non-vascularized medullary bone, as depicted on postcontrast T1 images.

Results of operative treatment of large benign proximal femur tumours

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In the orthopaedic clinic of Kaunas Medical Academy from 1987 to 1992, 11 children aged 5–13 years underwent operative treatment for large benign tumours of the proximal part of the femur. Seven had osteodystrophia fibrosa cystica and four had osteoblastoclastoma. Intralesional curettage and filling of bone cavities with small (0·05 × 1 cm) biocompatible osteoconductive polymer fibres was performed No post-operative immobilization was used. After lying in bed for 1 month, walking with a special functional device which decreases weight-bearing by two-thirds was allowed. and 4 months after operation full weight-bearing without any device was allowed Full consolidation was observed 5–6 months after operation

Self-reinforced tacks, pins and wires in the fixation of ligaments, osteotomies and fractures

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Seventy patients with total rupture of the ulnar collateral ligament of the first metacarpophalangeal joint were treated with a self-reinforced (SR)-PLLA mini tack The study comprised 23 women and 47 men of mean age 33·7 years A 1·1-mm channel was drilled in the base of the proximal phalanx at right angles to the axis of the bone through both cortices A 1·1-mm K wire was used to perforate the ligament. A PLLA tack (1·15 mm/15 mm) was placed through the ligament in the bone channel. The top 4 mm of the tack was pressed tightly against the cortex, and the device stabilized the joint immediately A dorsal plaster cast was used to immobilize the thumb for 4 weeks. Follow-up of 6–24 months showed 69 ligaments to have remained stable. The subjective result was good or satisfactory in 66 cases No inflammatory reactions were noticed. The mean time off work was 34·4 days. On the basis of these findings the new totally absorbable fixation method seems to be a reasonable alternative to metal wire fixation

A total of 27 patients with small-fragment osteotomies or fractures were treated by internal fixation with absorbable SR-PLLA pins. Follow-up was from 8 to 37 months. The two most common indications were chevron osteotomy of the first metatarsal bone for hallux valgus and displaced fracture of the radial head No redisplacement occurred and there were no signs of inflammatory foreign body reactions. Biopsies in two patients 20 and 37 months after implantation showed that no polymeric material remained. The results suggest that SR-PLLA pins are useful in small fragment fixations.

Finally, seven patients with a fracture of the olecranon and four with fracture of the patella had internal fixation with SR-PLLA pins combined with a SR-PLLA tension wire. The preliminary results seem to be good· one redisplacement of a patella fracture occurred. Further experience with these fractures is required before firm conclusions can be drawn

Biodegradable fixation in thoracic, vascular and craniofacial surgery

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Biodegradable osteosynthetic material made from self-reinforced polylactide has been used in ten craniofacial operations in Finland, in 14 such operations in Sweden (Clas Laurizen), and in six operations in Mexico (Antonio Fuente del Campo) without complication.

Biodegradable self-reinforced polyglycolide and polylactide has shown interesting possibilities when used experimentally to guide the regeneration of perichondrium to cartilage and for the fixation of experimental pectus excavatum in rabbits, this has led to successful clinical use of polylactide plates in three clinical pectus excavatum corrections.

In addition, the polylactide wire has successfully supported the healing of sternotomy in rabbits and pigs and has been used clinically to close median sternotomy in six patients Moreover, encouraging preliminary results have been obtained from the use of an extraluminal polylactide ring in supporting the healing of vascular anastomosis, namely aortoaortic anastomosis in the pig (This work was performed in collaboration with K. Verkkala and K Kyosola from Helsinki University Central Hospital.)

Limb exsanguination: comparison of three methods

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The effect of limb exsanguination by elevation alone, Esmarch bandage and Rhys-Davies' exsanguinator on the quality of the operative field in patients receiving upper- and lower-limb surgery has been investigated.

Patients were allocated to one of three methods of limb exsanguination using a randomized double-blind procedure The operating surgeon graded the operative field, using a previously published scoring system, without knowledge of the method of exsanguination employed Statistical analysis was performed with Fisher's exact test.

Mechanical exsanguination of the upper limb provided a satisfactory operative field in 28 of 34 cases while elevation alone was satisfactory in eight of 15. Mechanical methods involving the lower limbs were satisfactory in 33 of 38 cases compared with 15 of 20 elevated cases In the upper limb, suboptimal fields were associated with too much residual blood. In the lower limb, suboptimal fields from elevation were underexsanguinated, whereas those from mechanical methods were as likely to be overexsanguinated.

The authors advocate the use of mechanical methods of limb exsanguination where possible, but the clinically discernible advantages over elevation were not statistically significant.

Otorhinolaryngology

Surgical treatment of the discharging mastoid cavity

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Persistent otorrhoea following mastoid surgery is a frequent cause of morbidity, a considerable drain on outpatient resources and a possible pointer towards residual cholesteatoma

In an attempt to obtain a dry cavity, the authors offer revision surgery to patients with troublesome postmastoidectomy otorrhoea In a 4-year period, 37 patients, 20 men and 17 women of mean age 37 years, had such surgery. In all cases the mastoid bowl was cleared of granulations and the bony contours smoothed Cavity obliteration was attempted using a variety of techniques, alone or more often in combination, as follows local muscle flap (25), thiosite implants (12), autogenous bone plate (nine) and hydroxyapatite crystals (eight). Twenty-two patients had temporalis fascia grafting of the mastoid bowl and 11 had fascial grafting of mesotympanic defects The fascial ridge was lowered in seven cases and a modified cavity converted to a radical in four. Six patients had cholesteatoma at the time of revision and one had a mesotympanic cholesterol granuloma

Of the 32 patients available for follow-up two reported that their symptoms had been made worse by surgery, seven had little change and 23 now have a smaller mastoid cavity that requires minimal supervision

Revision surgery for the discharging mastoid cavity is associated with low morbidity and a good prospect of a satisfactory outcome

Middle fossa approach for acoustic neuroma: residual tumour, recurrence and growth rates

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Between 1980 and 1992 more than 250 acoustic neuromas of sizes between 5 mm (intrameatal) and 30 mm (measured within the cerebellopontine angle) were operated on by exposure via the enlarged mid-fossa approach. Postoperative surveillance of residual or recurrent tumour growth could be carried out by imaging techniques in more than 100 cases. Using computed tomography or magnetic resonance imaging measurements, the sizes of 20 tumours were monitored for more than 1 year before their complete removal or after partial resection

The recurrence rate of tumours after their virtual total removal was 1 0 per cent. Completeness of the excision can apparently be controlled by this approach in an excellent manner. Regrowth of residual tumours after deliberate partial resection did not follow firm predictions some remnants remained stationary over more than 6 years, others increased in volume, but with different rapidity, and some disappeared from the ordinary images. Furthermore, the tumour behaviour before surgical treatment cannot be predicted As a rough approximation, larger tumours grow more quickly than smaller ones Functional impairment of hearing did not correlate with an increase in tumour size

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Paediatrics

Middle cyst and fistula of the neck: results from surgical treatment of 128 children

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A total of 128 children with middle cysts and fistulas of the neck have been admitted to the regional Hospital of Haskovo, Bulgaria, between 1967 and 1992. Of these, 104 had an operation for middle cysts and 24 for middle fistulas; 51 (39·8 per cent) came with an uncertain diagnosis.

In all, 80 cases (62·5 per cent) had previously been treated in hospital, 33 by surgical operation. Recurrence occurred in 25 per cent of all cases.

Diagnosis was made by clinical examination supplemented by fistulography in 18 cases, cystography in 11, microbiological examination of secretions in 19, and ultrasonography in three. Histological examination was performed in all patients.

The patients were operated on by Sistrunk's method, 125 were cured and three had recurrence. The 30-day postoperative complications were: wound complications in 23 (18 per cent), paresis of the tongue in one, and cosmetic defects in three. Recurrence occurred in three cases within 1 year of surgery.

No complications were seen in 114 patients traced for up to 1 year, in 58 traced for 2 years, and in 13 traced for 10 years after surgery.

In summary, surgical experience indicates that the operation of Sistrunk appears to be the most successful approach to cure cysts and fistulas of the neck.

Diagnostic methods for functional disorders of the anorectum: suction biopsy, anorectal manometry, endoscopy and endoultrasonography

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Functional disorders of the anorectum in children are a frequent cause of admission. Successful treatment is possible only when a reliable diagnosis has been established.

Since 1970 four types of investigation have been used: (1) double-suction rectal biopsy for the diagnosis of aganglionosis and disturbances of innervation; (2) anorectal manometry for the diagnosis of functional disorders of the anorectum and for incontinence grading, (3) endoscopy for the diagnosis of morphological abnormalities, and (4) endoultrasonography for localization of the perirectal muscle layers.

Rectal suction biopsy identified 425 children with aganglionosis and 75 with neural dysplasia. Anorectal manometry enabled grading of severity of incontinence and revealed 'paradoxical reflex mechanism of the internal sphincter' as a cause of idiopathic constipation. Endoscopy allowed observation of complete or incomplete sphincter function. Endorectal ultrasonography (310 patients) demonstrated symmetrical or asymmetrical anorectal muscle layers or scars various distances from the anal verge.

Biopsy, manometry, endoscopy and endoultrasonography are all safe diagnostic procedures for the assessment of functional disorders of the anorectum with minimal discomfort to children.

Mechanical airway obstruction in children

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Airway obstruction in the paediatric population is an important cause of respiratory embarrassment and may be treated successfully with surgery if diagnosed early. A review was conducted of all 16 patients presenting to Our Lady's Hospital for Sick Children with airway obstruction since 1 January 1984 to the present to determine mode of presentation, demographic data, diagnosis, surgical procedure and outcome. All patients presented with stridor, 15 had recurrent respiratory tract infection and wheeze. The female:male ratio was 8:8. Mean age of onset of symptoms was 35·1 (range 0–90·4) months. Mean age at operation was 37·8 (range 1–112) months. Diagnostic tests included chest radiography, barium studies, angiography, bronchoscopy and bronchography. Airway obstruction was due to congenital tracheal stenosis (five patients), vascular ring (seven), bronchial stenosis (two) and vascular compression (two). Four of the patients with tracheal stenosis had congenital ring stenosis involving 50–70 per cent of tracheal length, and also had no major intracardiac abnormality. Surgical procedures included vascular ring division (seven), tracheal resection (six), sleeve resection of the bronchus (two), aortopexy (one) and lobectomy (one). All anastomoses were performed with absorbable polydioxanone sutures.

One patient died before surgery, 15 were operated on with two deaths (hospital mortality rate 13 per cent) both of whom had major intracardiac abnormalities corrected at the same time. Thirteen were discharged alive and well, one patient died 1 month after discharge from inoperable congenital heart disease and one patient has been lost to follow-up. The remaining patients are alive and well 1 month to 9 years after discharge with no respiratory symptoms and excellent growth of the tracheobronchial tree on bronchoscopy. In conclusion, all cases of persistent stridor should be investigated to rule out mechanical airway obstruction that is potentially amenable to surgical correction. Absorbable suture appears to allow excellent anastomotic growth.

Essentials of laparoscopic procedures in children

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For >10 years different minimally invasive methods for diagnosis and therapy in children have been evaluated. Endoscopy and especially laparoscopy play an important role. For 2 years laparoscopic operations performed with special paediatric instrumentation were compared with conventional procedures.

A laparoscopic set, designed and available for babies and children, was used for abdominal laparoscopic surgery for the following procedures: pyloromyotomy, adhesiolysis, liver wedge resection, appendicectomy, abdominal staging of Hodgkin's disease, large bowel resection and inguinal hernia. In children undergoing pyloromyotomy an endoscope was placed in the stomach at the entrance of the pylorus to aid localization of the pylorus.

In 2 years, 41 children aged from 10 days to 14 years have been treated by laparoscopy. All procedures planned as minimally invasive were performed without conversion to laparotomy. No postoperative complications occurred. All procedures were successful.

In the authors' opinion laparoscopic large bowel resection with a stapled anastomosis fulfills the criteria of being minimally invasive and easy to perform with minimal risk of postoperative adhesions and short postoperative ileus.

Open reduction and internal fixation of distal humeral fractures in children

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Fractures of the distal humerus are among the most common injuries in childhood. Accurate reduction is vital to achieve a satisfactory functional result and to avoid late complications. Therefore, the authors favour immediate operation with open reduction and internal fixation using two crossed K wires. Between 1979 and 1989, 72 children (mean age 9·6 years) underwent operation: 40 were treated for supracondylar fracture, 15 for unicondylar fracture, six for transcondylar fracture and 11 had complex fractures with dislocation of the elbow. The patients were examined at a mean of 53 months after injury. According to the classification of Morger, an ideal or good late result was found in 86 per cent. In none of these children did postoperative irritation of the ulnar nerve occur. It is concluded that open reduction and internal fixation of distal humeral fractures is superior to other methods; for example, the most commonly used methods of closed reduction and percutaneous fixation. Open reduction allows exact reduction, particularly correction of rotational displacement, and avoids varus deformity after trauma.

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Pancreas

Five cases of colonic complications in acute pancreatitis

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Acute pancreatitis may evolve locally, creating a series of complications such as pseudocyst of the pancreas, pancreatic abscess or obstructive icterus. Other complications include pancreatic ascites, intestinal obstruction and other colonic lesions

Between 1983 and 1986, 45 cases of acute pancreatitis have been treated, of which 14 (31 per cent) were necrohaemorrhagic. A significant group of our patients are holiday visitors with a high consumption of alcohol in a short time.

The diagnosis of colonic necrosis was on clinical and surgical grounds In three cases, an early radio-opaque enema with diluted water-soluble contrast was carried out, this showed colonic fistula clearly

The treatment of these cases was five necrosectomies with drainage of the transcavity and two transverse colon resections (Hartmann), two colostomies to the right and a colon segment resection with end-to-end fistula and protective colostomy to the right Colonic fistula as a late complication occurred in three cases

Colonic lesions due to pancreatitis are still a clinical rarity, but may be on the increase because of a better recognition Their aetiology is not certain but may include involvement of the portomesenteric axis by the pancreatic process through enzymatic, mechanistic and thrombotic effects.

Suppurative pancreatitis as a postoperative complication of acute necrotizing pancreatitis

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Two consecutive series of patients with acute necrotizing pancreatitis, submitting to surgery from 1975 to 1985 and from 1985 to 1992, were analysed. The first 72 patients underwent necrosectomy, peritoneal lavage, pancreatic drainage and treatment of biliary aetiology, when present, by cholecystectomy and biliary drainage, or cholecystectomy alone or cholecystostomy. In 26 patients postoperative pancreatic abscess occurred and was noted by change of the pancreatic drainage, which became purulent. An urgent reoperation was necessary in 21 patients, with death in 13 In the second series of 43 patients, necrosectomy was performed with wide exposure of the pancreatic area by debridement of all surroundings of the lesser sac, exposing the retropancreatic space Pancreatic debris, exudate and blood can easily drain to the dependent areas of the peritoneal cavity Drainage of the pouch of Douglas may be placed away from the pancreatic area, avoiding external bacterial contamination Biliary pathology was not treated at the first operation In the past 2 years a pancreatic instillation catheter was added to provide local broad-spectrum antibiotic therapy Postoperative suppurative pancreatitis occurred in only nine patients, necessitating seven reoperations; five patients died.

In conclusion, immediate reoperation should be considered whenever postoperative suppurative pancreatitis occurs In addition, peritoneal drainage should avoid the pancreatic area to minimize external bacterial contamination

Study of the influence of fresh-frozen plasma on the serum level of antiprotease systems in patients with acute pancreatitis

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Forty patients with acute pancreatitis were divided in two groups according to their mode of treatment. Both groups had standard treatment of acute pancreatitis but the patients in group 1 were given dried plasma while patients in group 2 were given fresh-frozen plasma (FFP) Serum levels of the antiprotease systems, α_1-antitrypsin and α_2-macroglobulin were measured.

α_1-antitrypsin was increased at a statistically significant level ($P < 0{\cdot}01$) from the first to the third day in both groups and remained high up to the seventh day The level of α_2-macroglobulin was low in both groups from the first to the third day. The α_1-antitrypsin level was not implicated in either prognosis or the severity of the illness

The α_2-macroglobulin level after 7 days of the disease was found to be statistically significant ($P < 0{\cdot}05$) in patients with severe septic complications compared with those given FFP, moreover, their disease course was very satisfactory It appears that administration of dried plasma does not alter the course of the disease

Role of cholecystectomy for microlithiasis in idiopathic acute pancreatitis

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Gallstones and alcohol abuse are common causes of acute pancreatitis (AP), accounting together for 70 per cent of all cases in Spain. Other aetiologies include trauma, hyperlipidaemia, surgery, endoscopic retrograde cholangiopancreatography and drugs. The remaining cases can be considered as idiopathic, while microlithiasis of the gallbladder has been proposed as a possible cause.

The purpose of this study was to assess the incidence of microlithiasis or biliary sludge in patients with AP initially considered as having idiopathic causes, and to evaluate the role of cholecystectomy in the clinical evolution of AP

In a series of 241 patients with AP, 130 (54 per cent) were attributed to gallstones, 60 (25 per cent) to alcohol, and ten (4 per cent) to other specific causes. The remaining 41 (17 per cent) were considered to be idiopathic These patients were submitted to a study of gallbladder bile obtained by contraction of the organ with a perfusion of 2 units Crick–Harper–Raper kg^{-1} of cholecystokinin The bile was collected through a soft gastroduodenal tube placed into the duodenum and was then centrifuged for 10 min. at 2000 r p m and examined with a polarizing microscope for microlithiasis Cholecystectomy was proposed to patients diagnosed with microlithiasis

Microlithiasis was found in 33 of 41 (80 per cent) patients Bile was normal in eight (20 per cent) Cholecystectomy was performed in 14 patients who agreed to surgical management and 18 did not have operation In the mean (range) follow-up period of 25·7 (1–52) months only one of the patients having operation presented with a new episode of AP, recurrence was seen in four (22 per cent) of those not undergoing operation

Microlithiasis of the gallbladder is found in 80 per cent of cases of AP initially considered to be idiopathic Cholecystectomy can prevent new episodes of AP.

Treatment of acute pancreatitis with octreotide

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Octreotide prevents the onset of acute pancreatitis (AP) and reduces the mortality rate from established AP in rats, but no convincing study in humans has been published The present study was designed to determine whether octreotide improves the course of AP in man Nineteen consecutive patients with AP (amylase level > 1000 units l^{-1}) were allocated to receive octreotide 250 μg subcutaneously and 0·5 $\mu\mathrm{g\,kg}^{-1}\,\mathrm{h}^{-1}$ by intravenous infusion ($n = 9$), or to be controls ($n = 10$) In all other respects treatment was standardized and identical Analgesia was by patient-controlled continuous infusion The groups did not differ with regard to Ranson or Glasgow scores on admission Clinical course was assessed by monitoring blood gases, haematology, biochemistry, clinical signs, radiology including computed tomography (CT) morphology and clinical milestones Although no severe cases of AP were admitted during the study period, prognostic falls in serum calcium (to $<2{\cdot}00\,\mathrm{mmol\,l}^{-1}$), albumin (to $<32\,\mathrm{g\,l}^{-1}$) and haematocrit (>10 per cent), and falls in

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haemoglobin (of $>2\,g\,dl^{-1}$) and oxygen saturations (to <10 kPa) were significantly less frequent in the octreotide-treated group ($P < 0{\cdot}05$, Fisher's exact test). Analgesic requirements were also significantly less ($P < 0{\cdot}05$, Mann–Whitney U test). Every other variable without exception including CT morphology showed a non-significant improvement in the octreotide-treated group. No deaths occurred in either group. These preliminary results suggest that octreotide may beneficially affect the course of AP.

Expression of gastrointestinal antigens and survival in resected pancreatic cancer

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Recent immunohistochemical and ultrastructural studies[1] have demonstrated that exocrine pancreatic tumours represent a heterogeneous cytological population with different immunophenotypic expression. Histological heterogeneity might be responsible for the different biological behaviours; this could account for the local recurrent disease in cases treated by radical excision and expected to have a better prognosis according to tumour node metastasis staging.

The expression of gastrointestinal antigens Du-Pan-2, M1 glycoprotein antigen, cathepsin E, pepsinogen II (PG II) and CAR-5 antigen has been retrospectively assayed by immunohistochemical methods in 70 cases of pancreatic cancer (66 ductal carcinoma, four cystadenocarcinoma) radically operated on. The antigenic expression has been correlated with tumour grading and survival.

Statistical evaluation was possible only for CAR-5 and PG II antigens. CAR-5 antigen was not found in any cystadenocarcinoma, and was expressed more frequently in G_3 (63 per cent) than in G_1 and G_2 carcinoma (40 per cent). PG II was expressed in all cases of cystadenocarcinoma, and was present in 43 per cent of ductal carcinoma. Mean survival correlated with antigen expression was 17·7 months in ductal carcinoma positive for PG II and 10·3 months in ductal carcinoma negative for PG II ($P < 0{\cdot}01$).

In conclusion, the data show that patients undergoing surgery for resection of ductal pancreatic carcinoma expressing PG II antigen have a more favourable prognosis. This information could be of value in planning treatment of pancreatic cancer.

1. Sessa F *et al.* Ductal cancers of the pancreas frequently express markers of gastrointestinal epithelial cells. *Gastroenterology* 1990; **98**: 1655–65.

Abdomen left open in severe acute pancreatitis

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Leaving the abdomen 'open' was undertaken in 64 patients with severe acute pancreatitis. The achievement of a 'stoma' between the outer space and the pancreatic bed was made possible by circumferential suture of the access slit in the gastrocolic omentum to the parietal peritoneum, with or without plication of the greater omentum at the inferior pole of the wound. Attachment of the omentum prevents leakage of the pancreatic fluid into the lower quadrants. Patients with an open abdomen did not require classic pancreatic bed drainage reoperation. Wide and constant access over the pancreas allows drainage of the pancreatic fluid and sequestrations, thus preventing retention problems as well as the hazards of repeated anaesthesia and operative procedures.

The open technique does not require special instruments, is technically easy to perform and lowers the mortality rate in acute pancreatitis.

Adjuvant external and intraoperative radiation therapy in resectable pancreatic cancer

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Prognosis after curative resection of carcinoma of the head of the pancreas is poor. Recurrence around the coeliac axis and mesenteric vessels occurs with high frequency. To improve local control a combined multimodality approach was started in January 1990 that includes surgical resection, intraoperative radiation therapy (IORT) and external beam radiation therapy (ERT). So far 12 patients have been treated in this way. In 11 cases subtotal pancreatectomy was performed, in one total resection. IORT has always been delivered to the tumour bed including the coeliac axis, portal vein and origin of the superior mesenteric vessels. Postoperative ERT of the tumour bed (dose 50 Gy; three-box technique) alone has been used in six patients (group 1), in six cases a preoperative treatment (the day before surgery, liver and pancreas irradiation, dose 5 Gy) was added (group 2). Mortality and postoperative major complications were absent, six wound infections occurred.

In group 1, five patients (stage I, two; stage III, three) died after a mean of 11·4 months: four from liver metastases (occurring after a mean of 6 months) without evidence of local disease and one from local recurrence outside the ERT/IORT field. One patient is disease-free at 3 months from surgery. All six patients in group 2 (stage I, one; stage III, five) are alive after a mean follow-up of 9·3 months without evidence of local recurrence, two have developed liver metastases.

Combination of ERT and IORT in the surgical resection of pancreatic cancer appears safe, tolerated and seems to offer a good local control. The high frequency of liver metastases suggests that more aggressive treatments (e.g. preoperative ERT, as in group 2) and/or chemotherapy need to be evaluated.

Predictive value of systemic manifestations in acute pancreatitis

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Organ and regional disorders in acute pancreatitis are connected with various clinical manifestations. Furthermore, when acute necrosis of the pancreas (ANP) occurs the pancreatic broth is responsible for some distinct systemic manifestations. From the records of 42 patients admitted with pathologically demonstrated ANP, 23 (55 per cent) were selected for a retrospective study on the basis of systemic manifestations. Initial shock was present in all 23 patients, acute respiratory distress syndrome (ARDS) in 14 (61 per cent), acute renal failure in seven (30 per cent), toxic psychosis in eight (35 per cent) and hypocalcaemia in one (4 per cent). Fourteen patients had three systemic manifestations, five patients had two and one patient had a single systemic manifestation. The most frequent and serious combination was initial shock and ARDS, occurring in 13 patients with eight deaths. Early surgical treatment for unmanageable initial shock was necessary in 11 patients (all presenting with ARDS as well) with five deaths. The overall mortality rate was 61 per cent, as nine of the remaining 18 patients died from septic complications. The statistical analysis of these data allows some conclusions: systemic manifestations occur early in about half of patients with ANP, and are associated with a poor prognosis which is even worse when a triple or double association occurs; patients developing systemic manifestations are candidates for early surgical treatment even though mortality is high and the outcome is complicated in patients who develop systemic manifestations following ANP.

Surgical internal drainage in pancreatic pseudocyst

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To evaluate the indications for and effectiveness of surgical cyst–enteric anastomoses, 70 patients with postnecrotic pancreatic pseudocyst were reviewed retrospectively. Elective internal drainage operations alone were carried out in 34 patients (49 per cent). Surgical procedures performed were pseudocystogastrostomy in six patients and pseudocystojejunostomy in 28 (Roux-en-Y limb in 27 and ω limb in one). The indications for elective surgery included persistent pseudocyst mass 4–6 weeks from the onset of pancreatitis, an uncomplicated course, mature pseudocyst wall detected by ultrasonography or computed tomography, ineffectiveness of other drainage procedures and minimal operative risk.

Postoperative complications requiring reoperation occurred in four patients (6 per cent) (intestinal obstruction in one case and suppuration of the residual cavity in one case). Pseudocyst recurrence was noted in two patients in whom the previous drainage procedure had failed because of stenosed anastomoses. They were cured by a second operation. There were no operative deaths.

It is concluded that pseudocyst–enteric anastomosis is the treatment of choice for persistent pancreatic pseudocyst with a mature wall. The appropriate surgical procedure is selected according to the site and anatomical relationships of the pseudocyst. The various procedures offer the same good results if the anastomotic diameter is more than 6 cm.

Allotransplantation of pancreatic embryonic tissue culture in treatment of complex diabetes

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Patients of age 15 to 46 years with a labile course of a severe form of diabetes complicated by microangiopathy and polyneuropathy, and in two cases also by retinopathy, were examined. All patients had disturbances of the immune system, whether a decrease in the absolute number of T lymphocytes, an imbalance in their subpopulations, the relationship between T helpers and T suppressors, high levels of the circulating immune complexes (up to 180 optimal units l^{-1}), or high plasma toxicity as assessed by the paramesial test.

Organospecific floating cultures of pancreatic cells of human embryos aged 16–24 weeks were used for transplantation. Cultures were transplanted into a large epiploon to all patients according to presently used methods. Maximal functional efficiency of the transplantate was observed at 16–20 days after surgery. Control examinations were made at 3, 6, 9 and 12 months after transplantation, at which times it was observed that the disease had clearly stabilized. Moreover, the postoperative ultrasonographic investigation of the transplantate morphofunctional state developed has shown the transplantate to remain highly effective for more than 1 year.

Comparison of two techniques of duodenum-preserving resection of the head of the pancreas in treatment of chronic pancreatitis

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This study compared two surgical techniques for treatment of chronic pancreatitis, both involving duodenum-preserving resection of the head of the pancreas. In a randomized controlled study, 12 patients underwent subtotal resection of the head of the pancreas as described by Beger[1] and 13 underwent resection of the head of the pancreas leaving a small remnant of pancreatic tissue combined with a longitudinal pancreatojejunostomy as described by Frey[2]. The time interval between onset of symptoms due to pancreatitis and surgery varied from 12 months to 12 years, with a mean of 4·6 years. Preoperative assessment of all patients included abdominal ultrasonography, computed tomography, digital subtraction angiography, blood chemistry, a pain score and quality-of-life index. Outcome measures were mortality, early and late morbidity, pain score, quality-of-life index and occupational rehabilitation.

The resected tissue showed a diameter of more than 5 cm in 76 per cent of patients. No postoperative mortality was observed in either group. Postoperative stenosis of the common bile duct in one of the patients in the 'Beger' group was the only complication that occurred, and was successfully treated using an endoscopically placed pigtail drain. When the Frey procedure was performed, the mean duration of operation was significantly shorter ('Beger' group 308 min *versus* 'Frey' group 194 min) and mean blood loss tended to be less ('Beger' group 1500 ml *versus* 'Frey' group 900 ml). In a mean follow-up of 12 months currently all patients reported substantial relief of the vast majority of symptoms. Evaluation of the quality-of-life index showed an overwhelming increase in patient contentment in both groups, in this aspect no significant differences were observed.

Both duodenum-preserving techniques of resection of the head of the pancreas resulted in alleviation of symptoms, including relief of pain, and caused a substantial increase in quality of life. In long-term follow-up, recurrence of symptoms and pain, alteration of glucose metabolism, as well as occupational rehabilitation will be assessed to determine the late results.

1. Beger HG. *Surgery* 1985; **97**: 467.
2. Frey CF. *Pancreas* 1987; **2**: 701.

Characterization of the procoagulant activity of human pancreatic carcinoma cell lines

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Carcinoma of the pancreas has long been known to be associated with a high incidence of thrombotic complications. Perhaps this ability of cancer cells to generate a procoagulant activity not only predisposes to thrombosis but plays an important role in tumour invasion and metastasis, as antithrombotic therapy at the time of implantation of certain experimental tumours reduces metastatic potential. The procoagulant activity of eight human pancreatic carcinoma (HPC) cell lines was studied 48 h after passage but before cells reached confluence. Tissue factor (TF) was measured in whole plasma by an amidolytic assay and recorded as thromboplastin units (TU) from a standard curve prepared using rabbit thromboplastin. Phosphatidylserine, considered to be responsible in part for monocyte adhesion and platelet activation by tumorigenic cells, was measured by prothrombinase activity (PA).

Cell line	TF dependent (TU per 10^4 cells)	TF independent (TU per 10^4 cells)	PA (pmol thrombin per min per 10^4 cells)
CaPanc 2	6560	100	22·9
Panc 1	60	10	23·6
BxPC 3	3450	50	14·4
MiaPanc	110	10	36·0
PT 45	2450	20	13·8
818·1	1400	0	17·2
818·4	14	0	14·7
818·7	4000	0	10·5

This study demonstrates for the first time that (1) the procoagulant activity of HPC is primarily dependent on expression of TF, (2) HPC cells vary considerably in the level of TF activity, and (3) PA is constant and independent of TF expression. These findings may explain the wide variation in thrombotic complications seen in patients with pancreatic carcinoma.

Mucinous cystadenoma and cystadenocarcinoma of the pancreas: a clinicopathological study

H. Levard, L. de Calan and H.C. Hennet, *French Association for Surgical Research, Colombes, France*

Mucinous cystadenoma of the pancreas is a rare cystic neoplasm that can change into pancreatic cystadenocarcinoma. This retrospective multicentre study (reviewing data from January 1978 to December 1987) reports the clinicopathological features and results of treatment of 27 patients with mucinous cystadenoma and 19 patients with cystadenocarcinoma.

There were 27 women with mucinous cystadenomas. The median age was 45 (range 23–72) years. Two patients each had two tumours. Twenty-five patients had a single tumour of mean size 9 cm, located in the head of the pancreas (three patients), body (four) or tail (18). One patient had a biopsy of the tumour only and one underwent cystojejunostomy. The tumour was completely excised in 25 patients; there were 22 distal pancreatectomies, one Whipple's procedure and two tumorectomies. There was no postoperative death, but two patients died from unrelated causes. The remaining 25 were alive and well at follow-up (median 20 months).

There were ten men and nine women with cystadenocarcinomas. The median age was 62 (range 49–82) years. The entire pancreas was involved in two patients, 17 patients had a single tumour located in the head (ten patients), body (six) or tail (one). Seven patients underwent curative resection and four palliative resection, eight patients had no resection and were treated by internal drainage and/or palliative bypass. There were two postoperative deaths. Twelve patients died from their tumour with a median survival of 10 months. Five patients were alive at 2, 3, 7, 26 and 62 months, two of whom had a recurrence.

The results strongly suggest that any mucinous cystadenoma of the pancreas, being a potentially malignant tumour, should be excised completely whenever possible. Moreover, pancreatic cystadenocarcinoma has a very poor prognosis which is similar to that of adenocarcinoma of the exocrine pancreas.

Microcystic adenoma of the pancreas (glycogen-rich cystadenoma): a clinicopathological study

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Microcystic adenoma of the pancreas is a rare cystic neoplasm that is benign. This retrospective multicentre study (reviewing data from January 1978 to December 1987) reports the clinicopathological features and results of treatment of 20 patients with microcystic adenoma of the pancreas.

There were four men and 16 women of median age 62 (range 31–82) years. The tumour was found incidentally in ten patients (during an operation for other disease in three and during abdominal investigation for other disease in seven) Ten patients had a palpable abdominal mass with or without abdominal pain One patient had two tumours; 19 patients had a single tumour of mean diameter 7 cm, which was located in the head of the pancreas (six patients), body (five) or tail (eight). Two patients underwent a tumour biopsy only The tumour was completely excised in 18 patients, a Whipple procedure was performed in four and distal pancreatectomy in 12 There were two postoperative deaths, of patients operated on for carcinoma of the colon or rectum. One patient was lost to follow-up. The remaining 17 were alive and well, without evidence of recurrence at follow-up (median 16 months)

The present results confirm that microcystic adenoma of the pancreas is benign and can be managed conservatively For tumours in the body or tail of the pancreas distal resection can be carried out However, surgical removal of tumours in the head of the pancreas may not be necessary if a diagnosis can be made by biopsy and examination of frozen sections, especially in elderly patients If there is gastrointestinal or biliary obstruction, bypass can be performed.

Surgery of acute alcoholic and biliary pancreatitis

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For necrotic alcoholic pancreatitis (group 1), surgery was carried out 10 days to 2 months from the onset of symptoms Treatment aimed to eliminate the various complications and included necrosectomy and treatment of pseudocysts. Of 123 patients, 48 required reoperation; 24 of these died

For acute biliary pancreatitis (group 2), in addition to procedures on the biliary tree, surgical intervention on the pancreas was used in 47 patients, of whom seven died

In group 1, treatment was successful in 85 per cent of cases, with a late mortality rate for necrotic pancreatitis of 18 per cent. In group 2 the mortality rate was 5 per cent. Life quality after 3 years was satisfactory in 91 patients (49 per cent) in group 1 and 189 (91 per cent) in group 2

Selective indications for total parenteral nutrition in patients with acute pancreatitis

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Between 1988 and 1992, 44 consecutive patients with acute pancreatitis received nutritional support consisting of total parenteral nutrition (TPN) within 48 h of admission Of these, 24 patients had one or two Ranson's criteria and 20 had three or more. Sixteen patients required operation and two died TPN duration was 3–52 days and 22 patients developed sepsis· 12 had intraperitoneal abscesses and ten had catheter-related sepsis with positive blood culture for *Staphylococcus epidermidis* In patients with sepsis, the mean number of Ranson's criteria was 3 4 and the mean duration of TPN 23 7 days. In non-septic patients these values were 2·0 and 12·5 days respectively In patients with one or two Ranson's criteria the mean duration of TPN was 11·8 days, the overall rate of septic events was 42 per cent (ten of 24) and the rate of catheter-related sepsis was 20 per cent (two of ten). In patients with three or more Ranson's criteria, mean duration of TPN was 24·3 days, overall sepsis was seen in 60 per cent (12 of 20), and catheter-related sepsis in 25 per cent (three of 12).

It appears that septic events are directly related to the number of Ranson's criteria and to the duration of TPN If TPN is necessary in severe acute pancreatitis, there is no evidence that it is useful in mild pancreatitis, because of the risk of catheter-related sepsis.

Serious factors in necrotizing pancreatitis

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Of 235 cases of necrotizing pancreatitis treated, there were 70 deaths (29 8 per cent) Analysis of the whole sample group enabled identification of significant factors that should be considered in establishing prognosis and appropriate therapeutic measures. These factors are as follows First, aetiology; necrotizing pancreatitis of alcoholic origin and that developed postoperatively and post-traumatically have a higher rate of mortality than that of biliary origin Second, being male, extremes of age and the presence of chronic disease (e.g. diabetes mellitus, pulmonary, liver or renal disease) show a higher mortality. Third, local and regional extension; the highest mortality rate is found in patients who develop extensive or total necrosis of the gland, peripancreatic necrosis, retroperitoneal extension and haemorrhagic ascites Fourth, sepsis; in cases of generalized sepsis within the peritoneum, necrotizing pancreatitis was associated with a higher mortality rate than in patients with an aseptic course Sepsis is implicated in the pathogenesis of multiple organ failure. Finally, clinical factors: refractory shock with early renal failure, neurological phenomena from extreme agitation to coma, and diffuse gastrointestinal haemorrhage are poor prognostic features.

Comparison between transplantation of pancreatic islet cells into liver subcapsularly and via the gastroduodenal vein in diabetic rats

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A total of 50 isogenic albino rats were use in this experimental study. Groups A, B and C each consisted of ten rats, group D, which consisted of 20 rats, underwent operation and total pancreatectomy was performed to obtain islet cells Groups A, B and C were rendered hyperglycaemic with streptozotocin (275 mg kg^{-1}), and islet cells were passed intraperitoneally into the liver via the gastroduodenal vein in group A rats, subcapsularly in group B rats, while group C was studied as the control group. The high blood sugar levels of the diabetic rats in group A started to decrease by the seventh day and after the tenth day they stayed at normoglycaemic levels ($P<0{\cdot}01$). In group B rats, islet cells were passed into the liver subcapsularly but blood sugar levels of this group of diabetic rats remained high throughout the study ($P < 0{\cdot}01$). Histological examination showed that viable islet cells were present in liver when islet cells were given via the gastroduodenal vein. When islet cells were injected under the liver capsule, in spite of detection of viable islet cells in liver on the first day by histological examination, significant lymphocyte infiltration under the liver capsule, and necrosis and abscess formation without any viable islet cells were noted on the 21st day.

In conclusion, isolated islet cells given via the gastroduodenal vein remain viable in liver and function well, regulating blood sugar levels effectively In contrast, no viable islet cells were demonstrated when the same islet cells were injected into liver subcapsularly, as blood sugar levels remained high in this group of rats

Endocrine tumours of the head of the pancreas and periampullary area

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Endocrine tumours of the periampullary area and the head of the pancreas may require an extended surgical procedure for cure. Since 1968, 37 patients have been observed with proven pancreatic endocrine tumours (PET). 19 insulinomas, nine Zollinger–Ellison syndrome (ZES) and nine non-functioning tumours.

Of the 19 insulinomas, 18 were typical single adenomas of the head of the pancreas and ranged in size from 1·0 to 4·0 cm. Fourteen were treated by local excision, two by pancreatoduodenectomy (PD) and two by subtotal resection of the head of the pancreas; all patients were cured. One patient had a multiple endocrine neoplasia syndrome (MEN I) and four adenomas were excised from the head of the pancreas, this patient is still normoglycaemic 8 years later.

Five of the nine patients with ZES had multiple tumours (two had MEN I) and three patients had microadenoma (< 0·5 cm). Five patients were treated by PD and four had excision of duodenal adenomas. In two cases ZES was not cured by surgery with one recurring 14 years after surgery. Five patients had normal gastrinaemia 5–16 years after operation. Six of eight patients with non-functioning tumours underwent resection: two PD, one partial pancreatic head and body resection, two local excisions and one partial duodenal resection. One died after 6 months from tumour progression, and four remain disease-free 1–11 years after operation. One of three patients with liver metastases was still alive 5 years after diagnosis.

While preservation of disease-free pancreas is generally the rule with insulinomas (extended procedures being reserved for technical problems) in the present series four of 19 patients had resection of the pancreatic head. Since long-term survival in non-beta PET is frequent, these tumours require an aggressive surgical approach even if advanced, as cure or long-term palliation can frequently be achieved.

Predictive factors in acute pancreatitis

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An attempt is made to identify the predictive factors of morbidity and mortality in acute pancreatitis. Data from patients with severe ($n = 75$) and mild ($n = 46$) pancreatitis were handled separately. The initial functional signs of predictive value ($P < 0{\cdot}01$) were predominantly epigastric pain, vomiting, fever, signs of peritoneal irritation, obstruction, jaundice, respiratory distress and encephalopathy. Initial leucocytosis, but principally its persistence, suggests the serious nature of the disease ($P < 0{\cdot}001$), as does the presence of hyperbilirubinaemia ($P < 0{\cdot}05$). Serum amylase levels can increase during the evolution of acute pancreatitis, but do not predict the prognosis. Among the associated lesions that suggested a poor prognosis were biliary lithiasis ($P < 0{\cdot}05$), pancreatic necrosis ($P < 0{\cdot}01$) and the appearance of a peritoneal inflammatory exudate ($P < 0{\cdot}001$).

Surgical treatment was addressed mainly to the pancreas and the biliary system, there was no significant statistical difference between the procedures. Reoperation was an unfavourable prognostic factor ($P < 0{\cdot}001$). There were 51 (42 per cent) deaths overall, 42 of which were among the 75 patients with severe pancreatitis. The highest frequency of death is during the first 4 days (56 per cent) due to shock (100 per cent), peritonitis (67 per cent), and intraperitoneal extension of cystonecrosis (31 per cent). Death in the second phase of acute pancreatitis was due to sepsis (77 per cent). Age over 55 years, hyperbilirubinaemia, peritonitis, leucocytosis, aetiology and shock were found to have a positive predictive value of death $>0{\cdot}5$.

This study, carried out in 121 patients operated on for acute pancreatitis, showed that morbidity and mortality rates depend on the severity of the disease and its complications.

Major haemorrhage from the pancreatic duct complicating chronic pancreatitis

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Acute haemorrhage is the most rapidly lethal complication of chronic pancreatitis (CP). If the pancreatic duct communicates with a pseudo-aneurysm, a haemorrhage into Wirsung's duct (HW) may occur. Diagnostic procedures, therapy and long-term results are still the subject of controversy.

Eleven cases of HW observed among 220 patients with CP are reported. Hospital mortality rate was zero, five patients died between 4 months and 8 years after treatment. In one case, total pancreatectomy was performed because of a histological diagnosis of diffuse pancreatic cancer after suture ligation and pancreatojejunostomy. Arterial embolization was attempted four times and was successful on three occassions. Three patients died from haemorrhage 2–8 years after successful treatment.

In conclusion, it is believed that embolization is the treatment of choice for HW, long-term results being satisfactory in three of four patients treated by this method. Subsequent gastrointestinal haemorrhage developed in one embolized and two surgically treated patients; only in one case was it documented as pancreatic. Emergency surgery can be performed with low risk for the patient if the correct diagnosis is timely or suspected. Left pancreatectomy or right pseudocystojejunostomy with wide drainage of the pancreas are preferred. External drainage provides inadequate drainage and usually requires further surgery.

Pancreatoduodenectomy and local excision in the operative treatment of ampullary carcinoma

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Carcinoma of the ampulla of Vater is a relatively rare tumour but represents 10–36 per cent of all surgically operable pancreatoduodenal tumours. Despite the fact that pancreatoduodenectomy (PD) continues to be considered as the operation of choice for resectable ampullary carcinoma, recent experience indicates that local excision (LE) of the tumour may be an acceptable alternative in selected cases. Reported are 23 patients with ampullary carcinoma who were treated by PD (pylorus-preserving in seven, standard in four), and LE of the tumour (12) during the past 14 years. The diagnosis of vaterian tumour was made by hypotonic duodenography (four), endoscopy with or without biopsy (11) or at operation (eight). Macroscopically the tumour was polypoid in 17 patients and ulcerating in the remaining six. None of the patients died in hospital. One died 9 days after discharge from cerebral haemorrhage. In the group of patients subjected to PD, five major complications were observed (pancreatic fistula, four; biliary fistula, one) compared with two (biliary fistula, one; rupture of duodenotomy, one) in the group with LE of the tumour. The 3- and 5-year survival rates were 57 and 40 per cent following PD compared with 50 and 50 per cent after LE.

Despite the limited size of the present series and the shortcomings of a retrospective review, it appears that LE of the tumour in selected cases of ampullary carcinoma of the polypoid type may offer results comparable to those of PD.

Recurrent pancreatitis in 160 patients

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Recurrence of acute pancreatitis ranges from 10 to 20 per cent in patients treated specifically, and from 20 to 40 per cent in those not treated. A total of 160 consecutive patients presenting with acute pancreatitis were studied and treated prospectively between April 1987 and January 1993. Of these patients, 110 had gallstones, 15 had had one or more attacks before undergoing treatment and one had had recurrence after treatment. Patients were divided into three groups according to the severity of the prognostic index, 0·0–0·2 being mild, 0·21–0·4 moderate and >0·41 serious.

In this series 34 recurrences were recorded in 16 patients (10 per cent) (more than two attacks per patient), 24 in patients with biliary lithiasis, eight in patients with idiopathic pancreatitis and three in patients with hyperlipidaemia. While 144 patients had only one attack of acute pancreatitis, 46 (29 per cent) had had a similar attack to the present one, but acute pancreatitis had not been proven. The first attacks ranged from mild to moderate (mean(s.e.m.) 0·20(0·05)) but there were three serious cases from the second to the third attack (0·27(0·06)) ($P < 0{\cdot}05$).

In our experience, biliary lithiasis is the most frequent cause both of acute pancreatitis (69 per cent) and of recurrence (71 per cent). Since the second and third attacks are more serious ($P < 0{\cdot}05$), no patient with acute pancreatitis and biliary lithiasis should be denied an operation and every case of acute pancreatitis should be considered to be caused by gallstones until proved otherwise.

Influence of DNA ploidy, pathological factors and serum CA19-9 on the prognosis of resected pancreatic carcinoma

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It has recently been suggested that DNA content may provide significant prognostic information about pancreatic cancer. Serial CA19-9 assays have been studied and also found to be related to prognosis after excisional surgery. Twenty-six consecutive specimens of resected pancreatic carcinoma have been analysed to assess the rate of aneuploidy and the relationship between survival, DNA pattern and histopathological features. All patients had serial CA19-9 assay before and after surgery.

Sections (50 µm) of primary tumours were prepared and analysed by fluorescence-activated cytometry. All patients had a ductal adenocarcinoma, 21 pancreatoduodenectomies and five left pancreatectomies were performed, 15 being radical operations and 11 with microscopic residual tumour. Twelve patients had a well differentiated tumour and 14 a moderately or poorly differentiated tumour. Ten patients were in stage I, four in stage II and 12 in stage III according to Union Internacional Contra la Cancrum staging. Twelve of 25 patients had lymph node metastases. In eight cases the primary tumour was aneuploid. Excluding three patients with preoperative low CA19-9 levels, ten of 23 had a fall of CA19-9 levels to normal range after surgery.

No relationship was found between size, stage, lymph node status or tumour grading and DNA ploidy. A postoperative fall of CA19-9 was significantly related to survival (P = 0·001), only one of ten patients with a low postoperative CA19-9 survived less than 12 months and only two of 13 with high CA19-9 survived more than 12 months. No relationship was found between ploidy and postoperative fall of CA19-9. Lymph-node status (P = 0·02) and stage (I *versus* II–III, P = 0·04) were found to correlate with survival.

Despite preliminary findings suggesting that DNA ploidy may have prognostic value in pancreatic cancer, a relationship between ploidy of the primary tumour and survival after surgical resection has not been confirmed. DNA ploidy is unrelated to the metastatic potential of the tumour, CA19-9, lymph node status and stage are the main factors influencing prognosis.

Radical resection for ampullary carcinoma: long-term results

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Cancers arising from the region of the ampulla of Vater have a better prognosis than tumours originating from the periampullary area. Several factors are known to affect survival after radical resection for ampullary carcinoma, but conflicting results have been reported. Experience with ampullary carcinoma is reviewed to identify pathological factors influencing survival after resection.

From 1970 to 1990, 30 patients underwent potentially curative resection for adenocarcinoma of the ampulla of Vater (25 pancreatoduodenectomy, one total pancreatectomy, four local excision). According to the Union Internacional Contra la Cancrum staging system 19 patients were stage I or II and 11 stage III–IV. Tumor size ranged from 1·1 to 5·2 cm, seven patients had lymph node metastases, nine pancreatic invasion. The tumour was well differentiated in 19 cases and moderately or poorly differentiated in 11. One patient died in the perioperative period (3 per cent). Overall 5-year actuarial survival rate was 37 per cent, 45 per cent in the absence of lymph node involvement *versus* 0 per cent with nodal metastases (P=0·03). Estimated 5-year survival rate was 51 per cent for well differentiated tumours (P = 0·001) *versus* 0 per cent for moderately or poorly differentiated tumours. Survival was significantly better (P = 0·0002) in patients with tumour of stages I or II than in those with disease of stage III–IV. Tumour size, pancreas invasion and jaundice did not correlate with survival. After local excision, two patients developed local recurrence after 6 months and 3 years. Among the 15 patients without nodal metastases and treated by pancreatoduodenectomy, local and hepatic recurrence were found after 3, 3, 4, 5, and 9 years respectively.

In conclusion, long-term survival may be obtained by radical resection in patients with ampullary carcinoma, but the risk of late tumour recurrence requires long and careful follow-up. Lymph node involvement, tumour differentiation and stage are the most important factors influencing long-term survival.

Adenocarcinoma of the head of the pancreas: importance of selection for curative resection

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Adenocarcinoma of the head of the pancreas still has a very poor prognosis since adjuvant therapy has not proved efficacious and surgical resection remains the only chance of cure. Despite progress in surgical technique and perioperative management, the mortality and morbidity rates associated with pancreatoduodenectomy (Whipple's procedure) are significant. Criteria for curative resection must therefore be clearly defined to select patients who could benefit from pancreatoduodenectomy.

Between 1 January 1981 and 31 December 1990, 80 patients were operated on for histologically proven adenocarcinoma of the head of the pancreas, periampullary and endocrine tumours were not considered. Twenty patients underwent pancreatoduodenectomy, 14 procedures could be considered macroscopically curative (wide *en bloc* resection with local lymph node dissection and no distant metastases). Histological examination confirmed that resection was curative in eight patients (margins were free of tumour and there was no vascular or lymphatic vessel invasion). The survival rate of patients in this latter group (group 1) was compared with that of those who underwent palliative pancreatoduodenectomy (group 2) or a primarily palliative procedure (biliary diversion and/or gastroenteroanastomosis) (group 3).

The median survival time of patients in group 1 was significantly higher (14·6 months) than of those in groups 2 (6·7 months) or 3 (7·1 months). Moreover, the 1-year survival rate for patients in group 1 was 50 per cent compared with 17 per cent in group 2 and 16 per cent in group 3. In group 1, 38 per cent of patients survived for > 24 months compared with none in group 2 and 7 per cent in group 3. The mortality rate was significantly higher in patients who underwent pancreatoduodenectomy (25 per cent) compared with those who underwent palliative diversion (8 per cent).

It is concluded that pancreatoduodenectomy is the only surgical procedure with curative potential, although significant mortality and morbidity rates limit its value. Staging of adenocarcinoma of the head of the pancreas should be more precise to select patients who will benefit from pancreatoduodenectomy and to avoid palliative resection. Preoperative laparoscopic examination with biopsies and peritoneal cytology, and routine peroperative ultrasonography should be evaluated as a means of achieving better staging.

Place for gastroenterostomy in patients with advanced cancer of the head of the pancreas

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There remains doubt about the need for gastroenterostomy in patients with advanced cancer of the pancreatic head, performed either prophylactically or when passage of food becomes impossible. The records of 142 patients admitted to the Erasmus University Hospital over a period of 11 years for advanced pancreatic cancer were reviewed. Preoperative and postoperative intake of food in cases involving gastroenterostomy and the morbidity and mortality rates associated with abdominal surgery in these patients were considered. Of 129 patients without symptoms of gastric outlet obstruction at the time of diagnosis, 31 underwent prophylactic gastroenterostomy. The procedure did not prevent gastric outlet obstruction in four patients. Of the remaining 98 patients, 15 developed gastric outlet obstruction. Cox proportional hazards analysis showed no significant difference in the interval to the occurrence of a symptomatic obstruction between these two groups, taking into account other covariables. Postoperative complications and mortality rates after gastroenterostomy were high, ranging from 9 to 41 per cent and 11 to 33 per cent respectively. These results do not indicate that prophylactic gastroenterostomy significantly prevents future gastric outlet obstruction; therefore, as it also increases morbidity rates, it should not be performed. Gastroenterostomy to relieve symptoms should be considered carefully, as the success rate is low and the procedure is accompanied by considerable morbidity and mortality rates.

Peptic ulcer

Restoration of nightly spontaneous alkalinization in duodenal ulcer using ranitidine

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The effect of a 2-week administration of ranitidine (150 mg twice daily) on 24-h pH profiles in eight patients with duodenal ulcer is described Healthy volunteers demonstrated spontaneous nightly alkalinization.

Patients with duodenal ulcer before treatment had a mean(s.d.) nightly period at pH > 4 of only 68·5(65·7) s This value increased to 114·07(39·43) min after treatment The mean(s e m.) proportion of the night with pH > 4 before and after treatment was 0·5(0·3) per cent and 27·6(10·0) per cent respectively, with a significant increase ($P = 0·05$) Ranitidine was able to induce ulcer healing even when used for only 2 weeks. Complete healing of the ulcer was seen in patients whose overall acidity time was reduced to almost 40 per cent of the value before treatment

Intravenous omeprazole *versus* ranitidine in bleeding duodenal ulcer: a prospective randomized trial

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Omeprazole is a potent inhibitor of H^+–K^+-ATPase activity, and provides a more effective treatment for acid-related diseases of the upper gastrointestinal tract than H_2 blockers. However, there are few reports of its use in emergencies This study reports the results of a prospective randomized trial of intravenous omeprazole *versus* intravenous ranitidine in bleeding duodenal ulcer

All patients were admitted as emergencies for upper gastrointestinal tract bleeding; diagnosis of bleeding duodenal ulcer was confirmed endoscopically in all cases After diagnosis, 21 patients (group 1) were randomly assigned to receive omeprazole (40 mg, bolus) followed by 80 mg day^{-1} as continuous infusion for the next 48 h. Twenty-four patients (group 2) received ranitidine (400 mg day^{-1}) as continuous infusion

Bleeding was stopped in 20 patients in group 1 (95 per cent) and in 17 in group 2 (71 per cent) ($P < 0·01$) Of seven patients in whom ranitidine treatment failed, subsequent omeprazole therapy stopped bleeding in five Operation was necessary in one patient in group 1 and in two in group 2 Control endoscopy performed at 15 and 30 days after bleeding showed complete healing of the ulcer in all patients given omeprazole and in 14 (82 per cent) of those given ranitidine Serum gastrin levels were not significantly increased after treatment. It is concluded that omeprazole seems to be effective in the control of bleeding duodenal ulcer.

Thoracoscopic truncal vagotomy

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A total of 15 men and seven women (mean age 40·2 (range 26–79) years) diagnosed with duodenal ulcer were treated by truncal vagotomy (TV) via left thoracoscopy over a period of 18 months Except for a woman of 43 years who was hospitalized 10 days earlier for a perforated ulcer that was treated by laparoscopic suturing, the diagnosis was made endoscopically Some 18 ulcers were located in the bulb and four in the first part of the duodenum, with 12 of these lesions penetrating deep posteriorly. The mean duration of the ulcer disease was 7·2 (range 3–13) years Four patients had a history of perforation. Of 13 patients who had experienced haemorrhage, eight had had a recent massive bleed.

TV was performed by left thoracoscopy through four cannulas (Half the patients had selective tracheal intubation and one-third required pleural drainage.) The mean operating time was 46·5 (range 30–115) min. Feeding was started on average 1·6 (range 1–3) days after operation. The mean hospital stay was 4·6 (range 2–9) days but only 3·6 days for the last ten patients. There was no mortality or morbidity. Return to work was achieved around day 15 (range 4–34) after surgery. All patients were seen between 30 and 45 days after operation. Some 20 patients had Visick 1 and two Visick 2 (slowing of gastric evacuation ameliorated by dietary modifications). No diarrhoea was noted Follow-up endoscopy confirmed healing of the duodenal ulcer in all cases. An upper gastrointestinal series showed good gastric emptying in 20 of 22 patients and slight stasis in two asymptomatic patients The mean follow-up was 6·8 (range 1–12) months. TV is a simple, fast and efficient procedure with minimal side-effects. The technique offers a credible alternative to initial medical management in terms of efficiency and cost.

Bleeding duodenal peptic ulcer: injection *versus* operation

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Duodenal peptic ulcer was recognized as the cause of bleeding in 98 patients presenting with signs of upper gastrointestinal bleeding and who underwent emergency endoscopy In 95 per cent of the patients bleeding was stopped by injection of thrombin, while five (5 per cent) required surgery due to failure of the injection procedure Of 93 patients previously injected, 16 (17 per cent) rebled The highest rebleeding rate was in the Forrest IA group (40 per cent), rates were lower in Forrest IIA (12 per cent) and Forrest IB (7 per cent) patients Of the rebleeding cases, 11 were successfully reinjected, while five underwent emergency surgery In general, injection sclerotherapy was sufficient in 81 per cent, but was successful in only 69 per cent of patients with visible vessel/Forrest IA and IIA bleeding. Spurting bleeding was confirmed in ten bleeding patients who required emergency surgery Nine patients in whom injection was successful underwent elective operation without active bleeding, the indication for surgery being localization of the ulcer and the calibre of visible vessel in the ulcer base

The mortality rate of all bleeding patients was 4 per cent. No patient died following endoscopic treatment alone Among patients undergoing elective surgery one died (10 per cent), while three of ten undergoing emergency surgery died.

It is concluded that injection sclerotherapy is a valuable method to arrest bleeding from duodenal ulcers. Patients with large visible vessels of the posterior duodenal bulb wall should be considered as candidates for elective surgery after successful primary injection

Perforated peptic ulcer

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A total of 109 patients, 82 men and 27 women, were surgically treated for perforated peptic ulcer between 1987 and 1991. The mean age was 47 (range 18–89) years The mean interval between the first symptoms and surgery was 18 h (range 3 h to 7 days). According to their previous history, patients were divided into acute (56) and chronic (53) perforations. Twenty cases were related to non-steroidal anti-inflammatory drug use.

Some 45 patients underwent a simple closure technique plus treatment with H_2 inhibitors. In the other 64 patients, truncal vagotomy with a drainage procedure was performed

The overall mortality rate was 3·6 per cent (four patients) All four patients were elderly with high-risk factors (American Society of Anesthesiologists grade IV) and long-standing perforations (more than 72 h). Although morbidity rates were similar in both surgical groups (10 per cent), there were four cases of postoperative bleeding in the simple closure group and three of postoperative gastric retention. One of the latter required reoperation.

A mean follow-up of 42 (range 15–72) months was performed in 78 patients, 27 simple closures and 51 vagotomies. According to the Visick scale, five simple closures (19 per cent) and nine vagotomies (18 per cent) were included in grades 3–5, with no statistically significant difference even when divided into acute and chronic perforations

Mortality is confined to high-risk patients The morbidity and recurrence rate were similar in both groups Either surgical technique is suitable for perforated peptic ulcer, as long as simple closure is followed by H_2 inhibitor treatment

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Combined endoscopic and surgical management in the therapy of acute and severe gastroduodenal haemorrhage

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A benefit of emergency endoscopy is that active gastroduodenal bleeding can be treated by sclerotherapy This decreases the rate of emergency surgery with its related high mortality rate The aim of this study was to evaluate whether early elective surgery can decrease the number of patients undergoing emergency surgery.

From 1983 to October 1992, 535 patients were admitted with signs of acute gastroduodenal haemorrhage Each underwent immediate emergency gastroduodenoscopy to identify the site and extent of bleeding

The patients comprised two treatment protocols· I, 1983–1985, 116 patients, II, 1986–1992, 419 patients. In both protocols haemostasis of actively bleeding sources was by injection of adrenaline alone or with polidocanol (1 per cent). Vital signs, age, concomitant disease, blood count, transfusion of blood (units per 24 h), site and activity of bleeding (Forrest classification) were documented. In protocol I, patients were treated either with emergency or elective surgery, or conservatively. In protocol II, patients were categorized after successful haemostasis as high or low risk for recurrent bleeding after endoscopy High-risk patients underwent early elective surgery within 12 h of emergency endoscopy High-risk parameters were defined as: chronic or acute ulcer with active Forrest IA, Forrest IB or Forrest II bleeding with visible vessel on the posterior wall of the duodenum or lesser curvature of the stomach within the blood supply of the gastroduodenal and left gastric artery. In protocol I, 32 patients (28 per cent) were classified as high risk and 84 (72 per cent) as low risk for recurrent haemorrhage In protocol II, 122 patients (29 per cent) were high risk and 297 (71 per cent) low risk

Due to early elective surgery after emergency endoscopy, emergency surgery rates were reduced from 12 9 to 7·6 per cent, and the mortality rate from 53 to 38 per cent. The overall rate of surgery increased from 31 per cent in protocol I to 37 per cent in protocol II, whereas the overall mortality rate fell from 12·1 to 5 5 per cent Mean age and numbers of patients with Forrest IA and IB bleeding, in shock, with concomitant disease or who needed >5 units of blood after emergency endoscopy were similar in both groups.

In conclusion, management of acute gastroduodenal haemorrhage with combined endoscopic sclerotherapy and early introduction of elective surgery (by classifying high- and low-risk parameters during emergency endoscopy for recurrent bleeding) may significantly reduce the rates of emergency surgery, rebleeding and overall mortality

Results of a coordinated medicosurgical approach to peptic ulcer haemorrhage

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Haemorrhage from a peptic ulcer is a medical as well as a surgical emergency A coordinated approach to the management of this condition has been established. Suitable candidates for surgery were selected at an early stage on the basis of haemodynamic and endoscopic criteria, a definitive operation was performed as soon as the haemodynamic situation was stable and within the first 48 h after admission The results in terms of rebleeding at > 48 h and mortality rate were analysed.

A total of 157 consecutive patients (mean age 67 (range 16–89) years) were admitted with a bleeding peptic ulcer over a 2-year period Thirty-one patients (20 per cent) underwent early operation Some 149 patients (95 per cent) were followed for a mean of 44 (range 35–58) months

	<30 days	≥30 days
Rebleeding	10 (6)	13 (9)
Death	11 (7)	54 (36)

Values in parentheses are percentages

Four patients who rebled at <30 days and two at ≥30 days were in the surgical group Six of the deaths at <30 days and two at ≥30 days were related to peptic ulcer disease. Only one death in the surgical group related to peptic ulcer

A mortality rate of 7 per cent at <30 days was achieved with a coordinated approach, with only two deaths (1·3 per cent) related to peptic ulcer at follow-up of 44 months However, a significant risk of rebleeding of 8·7 per cent persisted during this period.

Factors predisposing to further haemorrhage and mortality after bleeding from a peptic ulcer

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The mortality rate of haemorrhage from peptic ulcers has remained unchanged This is mainly attributed to rebleeding in an increasingly elderly population with more coexisting systemic disease. The value of clinical factors and endoscopic findings in predicting rebleeding and death was analysed

Some 157 consecutive patients with a bleeding peptic ulcer were admitted over a 2-year period. Of these patients, 19 died and 37 had further bleeding. The predictive value of each factor was determined by the χ^2 test with Yates' correction.

Significant predictive factors of further bleeding were shock (15 of 25 patients), a transfusion requirement of 4 units during the first 48 h (19 of 46) and endoscopic signs of recent haemorrhage (29 of 79) The combination of these factors was of no better predictive value than shock alone The number of coexisting illnesses per patient was strongly related to the mortality rate ($P < 0\,001$). Other significant factors indicative of increased mortality included being on steroids (six of 16 patients), onset of bleeding during hospital stay (ten of 31), alcohol (eight of 32), further bleeding (nine of 37) and more than 4 units transfused over the first 48 h (seven of 46).

Shock remains the most valuable sign in predicting further bleeding and is superior to endoscopic stigmata. The close relation between mortality rate and coexisting illnesses underlines the fact that many deaths result from non-peptic ulcer disease

Plastic and reconstructive surgery

Transpositional finger replantation in children

P. Brenner, A. Berger and B. Reichert

Multidigit amputations, especially in children, still represent a challenging problem with regard to restoring optimal sensorimotor hand function Often either the orthotopic finger stump or the separated digits is unfit for conventional replantation This condition makes transpositional reattachment imperative.

Heterotopic finger replantations are a seldom performed procedure in current replantation centres. The incidence in this institution is approximately 1 per cent. The survival rate among children in this study was over 80 per cent, better than the conventional 'take' rate The favourable finger transfer in our closed series of eight children was the D2-stump, followed by a substitution of the middle finger and, finally, creation of an expanding opposite grip on the ulnar side of the hand. Secondary corrective procedures have been performed in one-third of patients. To evaluate global hand function, score systems according to Millesi or Tamai were applied Over 65 per cent presented a 'good' subjective and objective hand function according to Tamai.

Transoral approach to the cranial base

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Access to midline lesions (such as tumours and congenital malformations) of the skull base, particularly those of the clivus and craniovertebral junction, may be obtained by a variety of techniques through the mouth. The authors' experience of over 280 cases has enabled them to formulate certain guidelines A direct midline approach is occasionally used for intradural tumours and mid-basilar aneurysms The advantage of this technique is that a pathological process will laterally displace the cranial nerve and the major vessels The disadvantage is the depth at which one is working and thus special bayonetted instrumentation of sufficient length is required, as well as illumination and magnification of the operating microscope

Abnormalities at the craniovertebral junction may be dealt with simply by upward retraction of the soft palate For lesions at the anterior foramen magnum, a midline split of the soft palate provides access The authors have developed the extended (open door) maxillotomy consisting of a Le Fort I maxillotomy combined with a midline soft and hard palatal split. This provides access to the skull base from the sphenoid and ethmoid sinuses down to the second or third cervical vertebral body. If the dura is penetrated, a wide bore lumbar drain is inserted for 5 days, to be converted into a lumboperitoneal shunt.

Cheek–temporal flap in reconstructive surgery of the head

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The cheek–temporal flap is useful for the reconstruction of skin deficit in the lateral and upper cephalic regions, and in particular in the fronto-temporal region. The limits are: superiorly, the upper temporal line; anteriorly, the temporal crest of the frontal bone and the lateral orbital margin, and posteriorly, a vertical line that passes immediately under the skin. The preparation of the flap does not create particular difficulties and its versatility allows large variation in size depending on the need Preparation takes place from above up to the zygomatic arch and can be extended to the cheek region to extend skin mobility The flap, which in the temporal region can be cutaneous or fasciocutaneous, can now be advanced or rotated depending on the case; the mobilization permits it to reach the frontolateral, parietal and occipital regions easily with satisfactory results regarding skin continuity and scarring, which remains nearly completely masked by hair The authors' experience regarding reconstruction after trauma or oncological excision is described, and the results are satisfactory both aesthetically and functionally.

Prosthetic reconstruction after chest wall resection for cancer

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A series of 20 consecutive chest wall resections with immediate prosthetic reconstruction has been performed in 19 patients over a 6-year period (1987–1992)

T_3 lung cancer (eight cases), local recurrence of breast cancer (seven cases) and primary tumours originating in the chest wall (five cases in four patients) were the indications for surgery Reconstruction was performed only for chest wall defects of more than three ribs not located in the scapular region Prosthetic materials were either Silastic sheeting (1·016-mm thickness) or GORE-TEX soft tissue patch (2-mm thickness)

There was no operative mortality. Postoperative complications were negligible and satisfactory respiratory function was preserved in all cases Complete control of preoperative pain was achieved in all patients. Six cancer deaths resulting from metastatic spread have been reported at follow-up, in one case a chest wall recurrence occurred at a site distant from the prosthetic implant

Reconstruction of external cervicofacial defects

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Reconstruction of large cervicofacial defects requires a lot of tissue, which local flaps often cannot offer One solution is the use of distant pedicled or free revascularized composite flaps Between January 1982 and July 1992, 142 large head and neck defects were closed in 139 patients A pectoralis major osteomyocutaneous flap was used in 86 patients (17 women, 69 men) and a free latissimus dorsi flap in 53 (18 women, 35 men) Most of the defects resulted from cancer resections. The pectoralis major was used for the chin, neck and parotid area and the latissimus dorsi for the area of the midface and orbit, and for combined craniofacial defects. The failure rate of procedures using the pectoralis major was about 7 per cent and of those using the latissimus dorsi 2 per cent. There were no serious postoperative complications or long-term sequelae from either donor site The most important advantage of the pectoralis major was the shorter operation time and that of the latissimus dorsi the unlimited range of motion. The disadvantage of using the pectoralis major was a higher failure rate and that of the latissimus dorsi the necessity for microsurgery

Mandibular rotation and radial free flap for oropharyngeal tumours

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Buccopharyngectomy by segmental mandibular resection and myocutaneous pectoral flap reconstruction is associated with swallowing and chewing problems A new approach is proposed using mandibular rotation and radial free flap. During 1990–1991, seven patients underwent surgery for carcinoma of the tonsillar region (four), base of the tongue (two) and posterior wall extended to the pyriform sinus (one), in the range T_2–T_3, N_0–N_1 by TNM UICC classification Three patients presented with recurrent disease after a full dose of radiotherapy (60 Gy), three had had no previous treatment and one had received adjuvant chemotherapy (bleomycin and 5-fluorouracil) Radical neck dissection was performed in three cases and suprahyoid dissection in the other four. All patients underwent tracheostomy and gastrostomy There was one bone necrosis at the site of mandibulotomy. Cosmetic results were good in all seven patients One patient had salivary incontinence, one was unable to swallow and five patients had no trouble swallowing Chewing capacity was absent, poor in another and good in the other five cases The tracheostomy was closed on the 13th and the gastrostomy on the 18th day after surgery

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The present results are compared with a series of patients previously treated by segmental mandibulectomy and myocutaneous pectoral flap reconstruction. Mandibular rotation provides excellent access for lesions of the posterior oral cavity and oropharynx. Immediate restoration of mandibular continuity and use of the radial free flap allows improved chewing and swallowing functions with satisfactory cosmetic results

Denatured muscle autografts in peripheral nerve repair in patients with leprosy

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Autologous muscle grafts were used to repair 41 mixed peripheral nerves (eight median, at the wrist, 33 posterior tibial, at the ankle) in 32 patients with leprosy who had total anaesthesia and analgesia of the area supplied by the nerve. The aim was to assess the effectiveness of this technique at restoring protective sensation to such patients. The study has been in progress since November 1989, and the clinical results to date will be presented. Follow-up ranging from 3 to 36 months indicates that the progress of sensory recovery after grafting is slow but encouraging, particularly in the recipients of grafts to the median nerve.

Long-term results of blood flow and sensitivity of flaps used for the reconstruction of facial soft tissues

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The aim of the present study was to determine the blood flow and cutaneous sensation of flaps after the repair of tumour-related defects of facial skin The mean postoperative interval was 62 months. A total of 50 restorations (27 local flaps, seven free skin grafts, six island flaps and ten microvascular grafts) were examined using laser Doppler flowmetry, two-point discrimination and a pain and thermal sensation threshold Measurements were performed on the flap surface, the donor site and the contralateral areas corresponding to the donor site and the former defect. Paired *t* tests were employed to assess statistically significant differences between the sites of measurement Results showed restoration of both blood flow and the two-point discrimination on the surface of local flaps, island flaps and free skin grafts to a level not statistically different from that of the corresponding area of the side not operated on. Only the pain and thermal sensation thresholds exhibited a significant increase in the group of local flap restorations. Large myocutaneous flaps showed complete loss of cutaneous sensation in seven cases, while partial restoration without normal two-point discrimination was found in the remaining three patients after a mean interval of 44 months. Flowmetry rates of myocutaneous flaps corresponded to those of the donor site and were significantly lower than those of the recipient site in the head and neck area

Microsurgically revascularized scapula grafts for midface/maxillary reconstruction

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In complex midface/maxillary reconstruction, microsurgically revascularized scapula flaps have proved to be very useful. Since 1988, seven osteocutaneous scapula flaps have been used for maxillary/midface reconstruction in the head and neck area in this clinic.

The vascular anatomy of the scapula region allows for many combinations of isolated or combined bony and soft tissue reconstructions In particular, perforating maxillary defects can be reliably closed in separate layers, for example in patients with hemifacial microsomia, and orthognathic surgery principles can be combined with microsurgical tissue transfer from the scapula region. Special problems regarding recipient vessels and insertion of dental implants in vascularized scapula grafts are discussed.

Surgical treatment of Fournier's gangrene: a study of 15 patients

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Fournier's gangrene is a synergistic infection that produces necrosis of the subcutaneous tissues of the external genital organs and perineum It is associated with severe systemic toxicity and a high mortality rate It requires early diagnosis and aggressive emergency surgical treatment

A series of 15 patients treated between 1983 and 1992 is reviewed All patients underwent urgent debridement and treatment with broad-spectrum antibiotics. A colostomy was formed in three patients, a suprapubic cystostomy in two cases and reconstructive procedures in eight The aetiology was long-term urethral catheterization (nine patients), perianal abscess (five patients) and urethral obstruction (one). The most frequently associated disease was diabetes mellitus (eight cases).

The treatment of the open area and the healing times were recorded.

	No. of patients	Duration of hospitalization (weeks)
Healing by secondary intention	7	6–8
Interment of the testicles	3	3–4
Gracilis muscle flap	2	3–4
Scrotal skin approximation and a graft on the penis	2	3–4
Split skin graft	1	2–3

There were no hospital deaths Urgent and aggressive surgical treatment, broad-spectrum antibiotics and advances in reconstructive procedures account for the excellent results of this series.

Reconstructive surgery has decreased mean healing times by half, and also the mean duration of hospitalization and morbidity.

Reconstructive and voice-formation operations in the treatment of malignant laryngeal tumours

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A complex set of operations for recovery of the above functions has been established and widely used. The principal distinction of the proposed methods is as follows: the tracheo-oesophageal shunt method uses the topographoanatomical and physiological approach to protect the upper respiratory tract from the contents of the oesophagus, and for functional larynx resections the remaining larynx–gullet structures are used in the recovery of the separate functions. Apart from this the usual methods of functional larynx resection and tracheo-oesophageal shunt in patients with total larynx removal have been used

In all, 420 of the above operations, including 167 reconstructive subtotal operations on the larynx and gullet, were performed according to the methods proposed, 127 voice-formation operations after complete larynx removal according to the methods proposed and 126 analogous operations according to common methods.

Analysis has shown that the total oncological survival rate was 73 5 per cent. Moreover, the use of these methods of surgical rehabilitation of the impaired functions is 7 2 per cent more effective than traditional approaches.

Portal hypertension

Evaluation and long-term results of mesocaval interposition shunts

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The ideal therapy for variceal haemorrhage would eliminate this life-threatening complication of portal hypertension and have no adverse effects on hepatic physiology. Mesocaval interposition shunts preserve hepatopetal blood flow

Thirty-five shunts were performed as an elective procedure from 1982 to 1992 in patients with cirrhosis and variceal bleeding. There were 24 men and 11 women, with a median age of 51 7 years The underlying aetiology of the varices was alcoholic cirrhosis in 31 patients and postnecrotic cirrhosis in four. The criteria of Child and Pugh were used to evaluate all patients. 21 were in grade A and 14 in grade B. All patients had had two or more episodes of acute variceal haemorrhage. The mean diameter of the knitted Dacron graft used was 14 (range 10–16) mm

Intraoperative portal pressure measurements showed satisfactory pressure reduction (mean 40 per cent) There were no deaths after operation Eight patients had postoperative complications, an overall morbidity rate of 23 per cent. two ascites, four temporary encephalopathy and two recurrent bleeding. At 3 months, angiographic (five cases), ultrasonographic (six) or scan (17) studies evaluated shunt patency. In one case an occluded graft was observed The actuarial survival rate was 82 per cent at 2 years and 66 per cent at 5 years It is concluded that the interposition mesocaval shunt appears to be an effective technique for the control of variceal haemorrhage, has important haemodynamic advantages and can be used in most patients for the control of variceal bleeding caused by portal hypertension. Moreover, this procedure can be considered as a solution before transplantation

Experience with distal splenorenal shunt in treatment of bleeding oesophageal varices

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In recent years the introduction of endoscopic sclerotherapy, transjugular intrahepatic portasystemic shunting and liver transplantation have changed the role of surgery in the management of bleeding oesophageal varices. Surgery is indicated in this unit only when there is a failure of sclerotherapy and the patient is not considered a candidate for liver transplant

During the past 6 years 61 patients underwent a surgical procedure in this unit, 24 per cent being admitted for bleeding oesophageal varices during this period In 31 cases a Warren shunt was performed The mean age of these 31 patients was 52 years. The aetiology of portal hypertension was: liver cirrhosis in 27 patients, liver fibrosis in one, and portal thrombosis in three. Emergency operations were undertaken in ten patients (32 per cent), whereas 21 (68 per cent) underwent elective operation

The operative mortality rate in the elective group was 6 per cent, two patients dying from hepatorenal syndrome and sepsis Postoperative mortality rate, when other techniques were used, was 41 per cent Postoperative recurrent bleeding was observed in five cases (16 per cent); two were treated medically and three needed reoperation (two underwent modified Sugiura technique and one had a portocaval shunt) without mortality Actuarial survival was 86 per cent, 64 per cent and 43 per cent at 1, 4 and 6 years after operation.

A significant number of patients still need a surgical procedure for bleeding oesophageal varices. The Warren shunt could be performed in half of these patients, even in urgent situations In the authors' experience the splenorenal shunt gives the best results regarding postoperative death and patient survival

Selection of patients for peritoneovenous shunting in therapy-refractory ascites by a reinfusion test

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A prospective study with a newly developed preoperative ascites reinfusion test (ART) as a selection criterion for peritoneovenous shunts (PVSs) in the treatment of therapy-refractory ascites is presented A total of 457 patients with massive ascites were studied (January 1984 to January 1990). After a period of 3 months with conservative management including water and salt restriction, diuretics and paracentesis, 69 patients (15 1 per cent) were considered for a PVS Severe disseminated intravascular coagulation, bloody and infected ascites, and severe heart and renal insufficiency were contraindications in some and reduced this number to 51 (11 2 per cent) selected for ART

After placement of a caval and peritoneal catheter connected by a peristaltic pump, reinfusion began at $100\,\mathrm{ml\,h^{-1}}$, was increased to $400\,\mathrm{ml\,h^{-1}}$ and was carried out for 3–5 days Thereafter, 16 further exclusions were necessary, resulting mainly from coagulopathy In all, 39 PVSs were placed in 35 patients over a period of 6 years (18 Cordis Hakim, 21 Denver). Twenty-one patients were Child–Pugh grade C. All had liver cirrhosis. Two (5 per cent) minor operative complications (bleeding) were observed. Operative mortality rate was 11 per cent Coagulopathy developed in one case (3 per cent) with a fatal outcome. Sepsis related to the device was observed in one case (3 per cent) The patient survived after removal of the PVS. In four cases (11 per cent) a shunt malfunction occurred requiring revision. At the time of review (January 1992), 15 patients were alive, 14 of them with a patent shunt and ten with no ascites The 5-year survival rate according to Kaplan–Meier was 41 per cent

In conclusion, the ART is a cornerstone for the selection of patients with refractory ascites for PVS. Careful implantation technique, and pre-operative and postoperative management, in addition to ART preoperative selection criteria, are good methods for improving postoperative results The final goal is to improve the quality of life of these patients who have predominantly end-stage disease

Mesocaval interposition shunt with narrow-lumen polytetrafluoroethylene prosthesis in cirrhotic patients with recurrent variceal haemorrhage: a prospective study

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In 1972, Drapanas introduced a mesocaval interposition shunt to treat bleeding oesophageal varices using an 18–20-mm Dacron prosthesis

Since January 1987, a narrow-lumen 8–10-mm polytetrafluoroethylene prosthesis has been used in 56 patients with failed sclerotherapy In 93 per cent of cases liver cirrhosis, mostly alcoholic, was the underlying disease, 26 patients were Child–Pugh classification grade A, 25 grade B and five grade C. Thus, 51 patients were treated electively and five as emergencies There were five hospital deaths (9 per cent), two in the emergency group due to liver failure The hospital mortality rate for the elective shunt was 6 per cent One postoperative shunt thrombosis developed. The post-operative resting portal perfusion was shown to be preserved in all cases The encephalopathy rate was 11 per cent There were five late deaths, thus the 5-year survival rate according to the non-parametric estimation of Kaplan–Meier is > 80 per cent

These results show that a narrow-lumen mesocaval interposition shunt has a place as a treatment of portal hypertension in patients with recurrent haemorrhage after endoscopic sclerotherapy and that it is an alternative to the distal splenorenal shunt

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Non-shunting surgery in portal hypertension

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Because of high postoperative morbidity and mortality rates of shunting procedures, ligation of oesophageal varices and oesophagogastric resection, the non-shunting type operation devised by Hassab and Sugiura was adopted. The operation is performed through an abdominal incision with the devascularization of the abdominal oesophagus and of the proximal half of the stomach, splenectomy and transgastric ligation of oesophageal varices are also performed. Surgical control of the source of bleeding and correction of hypersplenism and of the mechanical effects of splenomegaly are achieved, as is the maintenance of good portal perfusion of the liver Portal encephalopathy is avoided.

During 1980–1991, 231 patients with portal hypertension underwent operation, 36 by the method described Fourteen patients had cirrhosis and 22 had presinusoidal disease (85·7 per cent of patients with cirrhosis, Child B and C stages). Four of the 36 underwent operation while bleeding

There was neither iterative bleeding nor portal encephalopathy Postoperative mortality rate was 19·4 per cent, whereas the mortality rate after shunting surgery was 39 2 per cent.

Rectum and anal canal

Plasty of the greater omentum and rectosigmoidectomy for treatment of rectal prolapse

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The aim of this surgical technique is to recover good function of the large intestine and to reconstruct the permanent continence of the internal sphincter mechanism of the anal and perianal area. With the combination of rectosigmoidectomy and plasty of the greater omentum, excision of the whole rectal prolapse and the rectosigmoid, lifting of the whole of the anal- and perianal area and support of the pelvic floor is achieved

The surgical technique is done on a wide rectosigmoidectomy and end-to-end anastomosis between the ends of the descending colon and rectum. This is followed by mobilization of the greater curvature of the stomach from the pylorus to short gastric arteries The long stem of the greater omentum is brought down to the pouch of Douglas This stem is secured to the left lateral abdominal peritoneum. This securing begins from the upper left lateral abdomen Each stitch sews together deeply the lateral abdominal peritoneum, the middle taenia of the descending colon and this stem from the greater omentum After all these separate stitches have been placed, using 2/0 silk threads, they are carefully tied individually The end of the stem of the greater omentum is secured on the anterior wall of the dissected rectum, as well as on the anastomosis of the descending colon and rectum. After draining the pouch of Douglas the incision is closed in layers In May 1991, operation using this method was carried out on a 65-year-old woman who had been suffering for 3 years from a complicated rectal prolapse. The function of the sphincter mechanism of the rectoanal area as well as of the large intestine has fully recovered

A perineal approach to disabling rectocele: a series of 20 patients

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Rectocele is a common rectal disorder, its usual clinical presentation is a distressing outlet obstruction. Surgical treatments usually proposed are based on transanal procedures However, we believe that such an approach does not treat all the abnormal components found in a rectocele.

This study evaluated a perineal approach to rectocele: 20 consecutive female patients (mean age 52 years) have been operated on Outlet obstruction was present in 17 cases, with vaginal digitalization in nine Minor faecal incontinence coexisted in five cases Surgical procedures involved: (1) complete mobilization of the rectal wall, (2) careful concentric folding of the rectocele, (3) stitching of the rectal fascia, and (4) preanal levatorplasty.

Care was taken not to reduce the vagina, therefore no colpectomy was performed. Results of this approach have been clinically and radiologically evaluated with a mean follow-up of 16 months Morbidity was minimal, anatomical correction was obtained in 18 cases and one pre-existing dyspareunia was aggravated. Normal rectal evacuation was restored in 16 patients, while four had functional failures Associated anorectal disorders (anismus, colonic inertia) were identified in each of these four cases.

This study showed that the perineal approach to rectocele has specific value It corrects the different components of the rectocele, avoiding anal dilatation, restoring a more stable pelvic floor, without creating significant sexual discomfort It compares favourably with other proposed techniques

Smoking impairs wound healing and increases risk recurrence in both Crohn's and non-specific fistula *in ano*

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Between 1984 and 1992, 295 patients were treated for either fistula *in ano* or rectovaginal fistula. These patients presented with 526 fistulas, 375 of which were treated by the authors There were 141 smokers, of whom 43 (30·5 per cent) had a postoperative recurrence of their fistula and 154 non-smokers of whom 23 (14·9 per cent) had a recurrence ($P < 0{\cdot}005$). There were 236 patients without evidence of Crohn's disease, 125 were smokers Thirty (24·0 per cent) of these patients had a recurrence Of the 111 patients without Crohn's disease who did not smoke, only 14 (12·6 per cent) had a recurrence ($P < 0{\cdot}05$) Only 16 of 59 patients with Crohn's disease (27 per cent) were smokers. There were 13 recurrences in this group Nine recurrences occurred among the 43 patients with Crohn's disease who did not smoke ($P < 0{\cdot}0001$) The mean(s.d.) delay in complete healing was 3·8(5·4) months for patients without and 10·9(12·2) months for patients with Crohn's disease ($P < 0{\cdot}0005$). In patients without Crohn's disease, healing was delayed by a mean(s.d.) 5·1(7·2) months in smokers *versus* 2·4(1·8) months for non-smokers ($P < 0{\cdot}05$) However, for patients with Crohn's disease the delay in healing was 15·4(13·9) months in smokers *versus* 3·8(2·1) months in patients who did not smoke ($P < 0{\cdot}05$) It is concluded that smoking increases the risk of recurrence and delay in healing after an operation for fistula *in ano*.

Late results of postanal repair: a retrospective study

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In 1975 Parks described postanal repair (PAR) in the treatment of idiopathic faecal incontinence Although the short-term results are quite promising, the long-term outcome is still unknown. The aim of this study was to evaluate the long-term results after PAR During the time period 1984–1992, 38 patients underwent PAR (eight men and 30 women, median age 62 (range 17–77) years. Twelve patients presented with idiopathic faecal incontinence. Eight patients underwent PAR for persistent incontinence after rectopexy for rectal prolapse. The history of the remaining 18 patients revealed obstetric trauma without clinical sphincter defect ($n = 4$), rectocele repair ($n = 2$), surgical trauma ($n = 9$), traumatic injury ($n = 1$), anorectal malformation ($n = 1$) and low anterior resection ($n = 1$) Postoperative complications (<30 days) occurred in six patients (urinary tract infection, four; wound infection, two) The median duration of follow-up was 39 (range 4–94) months During the first year of follow-up PAR was successful in 24 patients In 22 patients this beneficial effect was observed soon after the operation (< 6 months) In seven of the 24 patients incontinence recurred after a mean duration of 16 months In 14 patients continence was never regained The final outcome was therefore good in only 45 per cent of the patients. No correlation was found between the history of the patient and the final result. Therefore, it has to be questioned whether other treatment modalities such as biofeedback are not more favourable.

Relationship between anal pressure and anodermal blood flow: the vascular pathogenesis of anal fissure

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The poor healing rate of anal fissures and their predilection for a posterior midline location have been attributed to insufficient blood supply at the posterior commissure It has been suggested that the increased activity of the internal anal sphincter further decreases the arterial supply The aim of this study was to investigate this hypothesis by evaluating the relationship between anal pressure and anodermal blood flow

In 148 consecutive patients (M:F 67:81, median age 50 (range 18–87) years) with various colorectal disorders, maximal resting anal pressure (MRAP) was recorded. Laser Doppler flowmetry was performed simultaneously to assess perfusion of the anoderm at the posterior midline using a Periflux PF2B laser Doppler flowmeter A significant correlation was found between MRAP and perfusion of the anoderm ($r_S = 0{\cdot}61$, $P < 0{\cdot}001$) Both measurements were also performed in controls ($n = 12$), patients with faecal incontinence ($n = 22$) and those with anal fissure ($n = 7$). Mean(s.d.) MRAP was significantly higher in patients with anal fissure (125(24) mmHg) than in controls and those with faecal incontinence (60(18) and 42(14) mmHg respectively, $P < 0{\cdot}001$ and $P < 0{\cdot}001$, Student's *t* test), whereas perfusion at the base of the anal fissure was significantly lower (0·43(0·11), 0·70(0·17) and 1·02(0·34) V, $P < 0{\cdot}005$ and $P < 0{\cdot}001$)

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In six patients with anal fissure both measurements were performed before and 6 weeks after lateral internal sphincterotomy. This procedure resulted in a significant decrease of mean MRAP (46 (range 33–63) per cent), which was associated with a consistent increase of anodermal blood flow (54 (range 20–125) per cent). These findings strongly support the hypothesis that anal fissures are ischaemic ulcers.

Surgical treatment of rectal prolapse: a randomized study

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Rectal prolapse (RP) is often associated with a functional outlet obstruction. There is some evidence that division of the lateral ligaments (LL) during rectopexy, performed for rectal prolapse, results in a higher incidence of constipation than if the LL are preserved.

Twenty patients with RP were randomized to undergo anteroposterior Marlex rectopexy with either division of the LL (group 1, n = 11, nine women, mean age 60 (range 52–71) years) or sparing of the LL (group 2, n = 9, seven women, mean age 64 (range 58–69) years). Preoperative and postoperative assessment was made of frequency of defaecation, straining, tenesmus, continence, anal pressure, anorectal sensation, balloon expulsion and evacuation proctography. The mean follow-up was 14 (range 6–24) months.

Continence improved in both groups. Postoperative symptoms improved significantly in group 2 ($P < 0.01$) compared with group 1. There was no statistical difference between preoperative and postoperative anorectal sensation or balloon expulsion test. All patients showed resolution of prolapse by proctography. These data suggest that division of the LL is followed by a higher incidence of constipation than if they are preserved.

Spleen

Conservative approach to post-traumatic spleen injuries

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This paper presents a retrospective study comparing the results of conservative treatment with those of splenectomy. A total of 29 post-traumatic spleen injuries were treated in this clinic. The diagnosis of rupture with intrasplenic haematoma was formulated clinically with ultrasonography in 13 cases; there were three ruptures with haematoma of the spleen and 13 spleen ruptures with haemoperitoneum. The mean period of hospitalization for the patients not having splenectomy was 19 days, and for those undergoing splenectomy 15 days Three of the 16 patients who underwent operations had complications Conservation of the spleen after abdominal trauma must be used whenever the local and general conditions of the patient allow. The immediate postoperative complications, as well as the later ones that result from depressed immunological status after splenectomy, are arguments in favour of the conservative attitude in splenic trauma

Role of splenectomy in the management of splenic trauma

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Ninety-four cases of splenic trauma (blunt, iatrogenic and penetrating) presenting between 1981 and 1991 were reviewed retrospectively The overall splenic conservation rate was 55 per cent, including cases managed conservatively and surgically The literature has been reviewed with the aim of determining why the rate was so low and recommendations for improvement are made.

It is believed that the most effective way to obtain a greater conservation rate is an early laparotomy with the surgeon performing splenic repair and avoiding splenectomy for most patients Only life-threatening associated injury requires splenectomy.

The success rate for splenorrhaphy should be very high if early operation is undertaken If there is prolonged conservative management before operation the success rate is much lower

The criteria for conservative management should be. (1) isolated abdominal or extra-abdominal injury with haemodynamic stability (no blood transfusion requirement of > 2 units), (2) absence of peritoneal fluid at repeated examination by computed tomography; and (3) observation of patients in an intensive care unit for the first 72 h If these conditions are not applied then early laparotomy is the only safe and effective alternative.

Partial splenectomy in children: an alternative to splenectomy in the pathological staging of Hodgkin's disease

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The key to staging laparotomy in children with clinically staged I or II Hodgkin's disease is to identify the extent of disease and therefore the radiation field required The staging laparotomy consists of coeliac, portal, aortic, mesenteric and inguinal lymph node biopsies, wedge and needle biopsy of both lobes of the liver and splenectomy After splenectomy in children there is an increased risk of overwhelming postsplenectomy infection (OPSI). To reduce the risk of OPSI and ensure an adequate staging of Hodgkin's disease in children, partial splenectomy may be an alternative, since the risk of understaging is less than 1 per cent.

Twelve patients, median age 12 (range 7–16) years, with clinically staged IA or IIA Hodgkin's disease underwent a staging laparotomy with lymph node and liver biopsies and partial splenectomy in which the lower part of the spleen was resected. All patients were treated with involved field radiation therapy: three patients received only 44 Gy radiation and nine received 25 Gy and two cycles of mitoxin, Oncovin, procarbazine, prednisone–Adriamycin, bleomycin, vinblastine, decarbazine.

The median postoperative stay was 7 (range 5–23) days. Morbidity consisted of a small bowel obstruction requiring relaparotomy in one patient. The clinical stage changed from IA to IIIA in three patients The final pathological stage was IA in five patients, IIA in four and IIIA in three During a median follow-up of 6 (range 4–10) years, one patient died from secondary leukaemia after 4 years The remaining 11 patients have no evidence of disease and none developed OPSI.

Partial splenectomy is a reasonable alternative to total splenectomy for Hodgkin's disease. In the future, laparoscopy with laparoscopic lymph node biopsy, liver biopsy and partial splenectomy may replace staging laparotomy in Hodgkin's disease in children.

Conservative treatment of the spleen: a review of 168 cases

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From 1983 to 1992, 168 cases of total or partial conservative treatment of the spleen were practised (92 for splenic trauma, 54 for splenic haematological disease and 22 for splenic cysts).

For splenic trauma, the indication for operation was haemoperitoneum For splenic haematological disease, the operation was indicated for splenomegaly and/or the increasing transfusion needs and hypersplenism Conservative treatment for splenic trauma included 66 partial splenectomies, ten electrocoagulations, ten autotransplantations and one gastric transposition of the spleen. Haematological splenic disease involved subtotal splenectomy keeping the lower pole in 53 cases and the higher pole in one case Splenic cysts involved 11 partial splenectomies resecting the lower pole in two cases, the upper half-spleen in two cases, the lower half-spleen in two others, the upper two-thirds in two cases, and three total pericystectomies keeping the lower pole in one case and the upper in two others. In the ten other cases there were seven cyst dome resections, one splenotomy and drainage for a central spleen cyst, two electrocoagulations and one case was sutured Two patients required reoperation, one for bleeding and the second for necrosis. No death was reported in relation to the conservative techniques. The efficacy of partial splenectomy in the postoperative period was confirmed by Jolly's bodies measurements (absent in 122 cases), platelets increasing (negative in 123 cases), spleen homogeneity on ultrasonography (131 cases) and scintigraphy (fixed in 124 cases)

In conclusion, conservative treatment has proved to be a safe technique with definite benefits.

Splenectomy and haematological disease

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The purpose of this study was to evaluate splenectomy in patients with haematological diseases Between 1976 and 1992 a total of 35 patients underwent splenectomy for the following haematological diseases. thrombocytopenic purpura (12), haemolytic anaemia (five), chronic lympholeukaemia (seven), chronic myeloleukaemia (five), chronic monocytic leukaemia (one), Hodgkin's disease (four) and hypoplastic anaemia (one) There were 21 men and 14 women with a mean age of 33 (range 13–71) years All patients were treated by haematologists before operation for periods ranging from 1 week to 13 years. Indications for splenectomy were the failure of conservative treatment or cytopenia.

Midline laparotomy was used in 24 cases and oblique incision in 11 cases Two patients died (6 per cent) during the immediate postoperative period because of coagulation disorders with diffuse bleeding Five patients (14 per cent) had postoperative complications (pneumonia in three, wound infection in one, and superficial vein thrombosis in one) After splenectomy all patients' general and haematological states improved and haematologists continued their treatment

In conclusion, splenectomy has an important role as palliative management in patients with haematological diseases

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Results of splenectomy for idiopathic thrombocytopenic purpura: a review of 72 cases

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Seventy-two patients underwent splenectomy for idiopathic thrombocytopenic purpura (ITP) between 1979 and 1990. There were 14 men and 58 women. Mean age at splenectomy was 36·4 (range 11–73) years. Indications for splenectomy were steroid dependence in 21 cases and resistance to steroids in 44 cases. Thirty-five patients underwent platelet kinetic studies by ^{51}Cr-alloplatelets; 22 had splenic sequestration. Haematological results were evaluated on discharge, at 3 months and in the long-term (median follow-up 5·4 years) There was no mortality; morbidity was observed in 7 per cent. None of the patients experienced secondary infectious complications; 89 per cent had good results on discharge (platelets $> 120 \times 10^9 l^{-1}$), 73 per cent at 3 months and 90 per cent on long-term follow-up. Factors associated with a good response to splenectomy included a high postoperative platelet count ($> 120 \times 10^9 l^{-1}$ on discharge), younger age (under 30 years) at the time of surgery, preoperative steroid dependence and splenic sequestration. It is believed that splenectomy is the best treatment for ITP when a durable response with steroid therapy cannot be achieved.

Results of spleen conservation during distal pancreatectomy

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Resection of the body of the pancreas for chronic pancreatic disease generally includes splenectomy. In this series of patients the results of splenic conservation were studied, with a 1–3-year follow-up. Five patients underwent distal pancreatectomy for chronic pancreatitis, insulinoma or solid papillary tumour In all cases the main splenic vessels were ligated The spleen was preserved and remained vascularized through the gastroepiploic and short gastric vessels. Postoperative studies included blood count, ultrasonography and scintigraphy of the spleen, computed tomography (CT) of the upper abdomen, as well as Doppler investigations of the spleen.

All patients showed a peroperative blue-purple discoloration of the spleen. Postoperative ultrasonography and CT revealed swelling of the spleen with heterogeneous zones; blood investigations showed neither increased cytological breakdown nor any rise in thrombocytosis or leucocytosis. Vascular duplex scan showed increased flow in the short gastric vessels and virtually normal intrasplenic vascularization. In the long run, no clinical abnormalities were related to the main arteriovenous devascularization of the spleen.

In this small series of patients operated on by means of distal pancreatectomy with ligation of the main splenic artery and vein, no clinical effects were noted due to the devascularization Radiological, cytological as well as duplex parameters after operation showed no apparent deleterious effects in splenic function, as well as maintenance of adequate blood flow to the spleen.

Thoracic surgery

Surgical treatment of pulmonary metastases: experience with stapler and laser in the treatment of 100 patients

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Between 1983 and 1993, 100 patients with metastatic neoplasms of the lung underwent a total of 129 operations. The primary lesions were malignant neoplasms of the colon, breast, soft tissues, bones, epidermis (melanoma), uterus, ovaries, thymus and lung Surgery was performed using staplers or the neodymium–yttrium–aluminium garnet laser. There was no mortality related to the surgical procedure.

A prerequisite for surgery was the absence of other metastases and adequate pulmonary and cardiac reserve In some patients more than one thoracotomy was performed, up to a maximum of eight Postoperative chemotherapy was generally given

Long-term results of operation for non-small cell cancer of the lung

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Up to 1992, 1059 patients, selected from a total of 2614 observed cases, underwent surgery for lung cancer There were 278 pneumonectomies and 525 lobectomies and minor resections, the number of exploratory operations was 30 per cent before 1981, 21 per cent from 1982 to 1986 and less than 10 per cent from 1987 Mortality rate was around 5 per cent; 16 patients were lost to follow-up Long-term survival was considered for patients operated on within 1982 (184) and 1987 (263). More than 73 per cent of those with T_1N_0 disease fared well after 5 years, the figure was 57 per cent after 10 years Survival with T_2N_0 disease was respectively 50 and 27 per cent; T_3N_0 patients survived to 5 years in 34 per cent of cases, but after 10 years only 11 per cent of them survived A high percentage of the late deaths (around 50 per cent) was related to the development of metastases. Local recurrences were not frequent, a second primary carcinoma was observed five times The results of surgical resection could improve in coming years, due to the increasing number of patients subjected to neoadjuvant therapy.

Resection of pulmonary nodules using video-assisted thoracic surgery

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The aim of the study was to assess the limits and complications of video-assisted thoracic surgery (VATS) Twenty patients (16 men, four women, mean age 57 (range 17–80) years) underwent a total of 21 VATS procedures Indications for surgery were· primary malignant tumour (11 patients), benign lesion (five patients), and metastasis (four patients). A thoracotomy was performed twice after failure of VATS (one central pulmonary nodule and one pleural adhesion) One patient underwent two consecutive VATS procedures because the first removed insufficient tissue. The nodule was difficult to localize in 12 patients

Mean diameter of the resected nodules was 2 3 (range 1·5–5) cm. In total, 13 wedge resections, two segmentectomies and five lobectomies (two through a thoracotomy and three through a small 'utility' thoracotomy) were performed Among 11 patients operated on for a primary malignant tumour, seven had severely impaired lung function with a mean forced expired volume (FEV) of 1 litre Of these, five underwent wedge resections, one segmentectomy and one lobectomy through a 6-cm thoracotomy.

No death occurred There were two complications one persistent pulmonary fistula and one pneumonia Mean duration of chest drainage was 2 9 (range 0–10) days Mean duration of hospital stay was 5 5 (range 1–12) days

In conclusion, VATS is advised for benign pulmonary lesions and for frail patients.

Spontaneous pneumothorax: video-assisted thoracic surgery *versus* thoracotomy

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The aim of this study was to compare video-assisted thoracic surgery (VATS) with thoracotomy in the treatment of spontaneous pneumothorax. Thirty patients underwent VATS Pleurodesis was carried out using a 'scotch brite' swab. Blebs were stapled and resected

Thirty patients (23 men, seven women, mean(s.d.) age 37(18) years) previously having had open thoracotomy for pneumothorax were selected at random from the hospital files Patients were matched for age, sex, profession, smoking habits and disease aetiology

Eighteen middle-sized and five large-sized blebs were resected An independent physician telephoned the patients to assess postoperative pain and time off work. Mean(s d) chest drainage time was 6 7(4) days for thoracotomy and 5(2) days for VATS (t = 1·74, 29 d.f., P = 0 13) Mean(s d) duration of hospital stay was 11(5) days for thoracotomy and 7(2) days for VATS (t = 3 47, 29 d.f , P < 0 003). From day 30 to day 60 after surgery, pain was moderate in 28 patients in the VATS group and intense or acute in 21 of those in the thoracotomy group ($\chi^2 = 26$, 2 d.f , P < 0 001). Mean(s.d.) resumption of working was 2 6(0·8) months in the thoracotomy group' *versus* 1(0 8) months in the VATS group (t = 7 78, 29 d.f , P < 0 001). One persistent and partial pneumothorax was noted in each group and one relapse occurred in the VATS group ·5 months after surgery In conclusion, VATS produces a better quality of life and is as efficient as thoracotomy in treatment of pneumothorax

Adjuvant therapy in lung cancer after cytological and immunocytological detection of tumour cells by intraoperative pleural lavage

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According to the tumour node metastasis (TNM) classification, a malignant pleural effusion equals a T_4 spread of lung cancer The criterion is the cytological demonstration of tumour cells The results of a prospective study are presented in which pleural lavage was performed with 300 ml physiological saline solution after opening the chest to discover whether tumour cell dissemination into the pleural cavity had occurred in the early stages of lung cancer (lavage 1). A second lavage after resection of lung cancer (lavage 2) showed whether surgical manipulation of the lung parenchyma led to tumour cell contamination of the pleural cavity

A total of 205 patients (159 with the first manifestation of lung cancer, 46 with non-neoplastic lung disease) underwent pleural lavage The lavage fluid was prepared for cytological examination The sediments from the lavages were studied immunocytologically with the alkaline phosphatase–anti-alkaline phosphatase method Antibodies against keratin (Kl 1), vimentin (V 9), the endothelial marker BMA 120 and HEA 125, the B 72 antibody, polyclonal antibody against carcinoembryonic antigen (CEA) and a monoclonal antibody against CEA (BMA 130c) were used.

Tumour cells were found in lavage 1 in 65 patients and in 58 of them also in lavage 2. Among those previously classified as stage I ($pT_1 N_0$, $pT_2 N_0$), lung cancer-positive tumour cell detection was possible in 38 5 per cent of cases All controls were negative, i e there were no false-positive findings Immunocytological examinations found co-expression of Kl 1 and BMA 120 in squamous cell carcinoma and co-expression of Kl 1 and BMA 130c in adenocarcinoma of the lung, if pleural lavage was positive. The cumulative 4-year survival rate for curative resected non-small cell lung cancer of stage I (n = 78) was 22 1 per cent if lavage was positive (n = 30), and 64·3 per cent if lavage was negative (n = 48) (P < 0 05)

Detection of tumour cells in pleural lavage before resection proves that tumour cells have spread into the pleural cavity Therefore adjuvant therapy is necessary for patients with positive intraoperative pleural lavage in lung cancer

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Combined videothoracoscopy and limited thoracotomy

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The superiority of videothoracoscopy over standard thoracotomy in the treatment of small lesions of the pleura and the lung is now well accepted because it offers a short period of surgical drainage, minimal postoperative pain and early recovery In addition, videothoracoscopy often obviates the need for thoracotomy Nevertheless, in some cases it is still necessary to perform a standard thoracotomy, especially to manage any intraoperative complications.

Between September 1990 and February 1993, 15 wedge resections and two lower lobectomies were performed by videothoracoscopy In the latter two patients, however, it was necessary to perform a small incision (7 cm) on the route of the grasping forceps to have more control on the inferior pulmonary vein and to have an adequate exit for the resected lobe

In summary, it is believed that the combined videothoracoscopic procedure with a limited thoracotomy incision offers an excellent view of intrathoracic structures, and enables avoidance of the use of a rib spreader.

Diagnostic and therapeutic open lung procedures in patients with leukaemia and severe aplastic anaemia

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Pulmonary complications often occur in patients with leukaemia and severe aplastic anaemia (SAA). Such complications account for a significant number of deaths, especially in patients having undergone bone marrow transplantation (BMT). A retrospective study is presented of experience with 27 consecutive patients (17 men, ten women, mean age 30 years) operated on between 1980 and 1992 Twelve patients underwent open lung biopsy (OLB) and 16 lung resection (LR), one patient was operated on twice Results of surgical procedures are shown.

	BMT (*n* = 12)	Leukaemia (*n* = 8)	SAA* (*n* = 7)
Radiologically diffuse disease	5 (42)	3 (38)	0 (0)
Non-specific histology	10 (83)	4 (50)	1 (12)
Proof of causative micro-organisms	1 (8)	3 (38)	6 (75)
Ratio of OLB to LR	8 4	4:4	0.8
Mortality (30 days)†	6 (50)	3 (38)	0 (0)

Values in parentheses are percentages *Eight operations, †no death due to operative procedure

In conclusion, when considering an open lung procedure in patients with haematological dysfunction it is helpful (for prognostic reasons) to distinguish between the categories BMT, leukaemia and SAA. Based on present findings open lung biopsy is no longer advocated in patients undergoing BMT with (acute) diffuse lung disease, as diagnostic yield is limited and seems to have little or no influence on outcome. Lung resection in localized disease, especially in patients with SAA, is beneficial in most cases.

Indications and results of operation for small cell lung cancer

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Between 1982 and 1991, 31 operations were performed for small cell lung cancer. The mean age was 57·3 years Patients were operated on with a preoperative diagnosis of bronchogenic cancer (small cell cancer, ten; undifferentiated carcinoma, four, adenocarcinoma, one). Only four patients were treated before operation by chemotherapy or radiation. At diagnosis 23 patients were classified as stage I, two as stage II, four as stage IIIA and two as stage IV On five occasions only a diagnostic exploration operation was possible Resections included 16 lobectomies, four wedge resections, three pneumonectomies and three bilobectomies After operation only 14 patients were stage I, two were stage II, 12 were stage IIIA and three were stage IV Three postoperative deaths occurred: one as a result of cardiovascular failure, one because of lung embolism and one because of bronchial fistula after pneumonectomy. Postoperative treatment in 21 patients consisted of either chemotherapy (ten), radiation (one) or both (ten) Until now after a mean follow-up of 27 months, 14 patients have died between 3 and 25 months after operation, in 11 cases because of tumour progression, and ten patients are alive with a maximum survival of 72 months Three patients were lost to follow-up It is concluded that resection of small lung cancer is indicated as primary management for all patients with a tumour in stage I and II, and as secondary therapy for all patients with a tumour in stage IIIA and good remission after chemotherapy and/or radiotherapy

Experimental study of tracheal anastomosis

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Revascularization of tracheal segment implants with omentum is possible. Previous trials by the authors have proved that the best results are achieved when the trachea is kept distended, its lumen drained, and the recipient receives immunosuppressive therapy with antibiotic prophylaxis.

The purpose of this trial was to test the different types of anastomosis using this experimental model A total of 50 Sprague–Dawley rats were used, and tracheal extraction from the donors performed by median sternotomy. The trachea was divided in two parts, performing anastomoses of hemitracheas from two different donors The implant was distended by traction from its zenith, its lumen was drained, and it was implanted into the omentum of the recipients via a laparotomy. Three groups were studied. end-to-end anastomosis group (*n* = 20); telescoping group (*n* = 20), and the control group with normal tracheas (*n* = 10) Groups 1 and 2 received immunosuppressive therapy (cyclosporin and azathioprine) and antibiotic prophylaxis (cefonicid). After 14 days the animals were killed and tracheal anastomotic segments studied and histologically graded according to a previously established scoring scheme (0, normal, 9, necrosis) Non-parametric statistical analysis was performed using the Kruskal–Wallis test

No statistically significant difference was found when the groups were compared The transplanted and anastomosed tracheas of group 1 had a normal microscopic appearance, even at the site of anastomosis However, group 2 showed moderate necrosis of the telescoped cartilage, whereas the anastomoses appeared normal

It is concluded that omentum promotes complete revascularization of anastomoses of transplanted trachea when its collapse is avoided, the lumen is drained, and the recipient receives standard immunosuppression, regardless of the type of anastomosis used

Intrathoracic muscle transposition in the treatment of chronic postpneumonectomy bronchopleural fistula

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The management of postpneumonectomy empyema (PE) associated with bronchopleural fistula (BPF) remains controversial The aim of this study was to assess the effectiveness of a sequential procedure Twelve men (mean age 57 (range 40–65) years) with PE and BPF were treated. The initial diagnosis was bronchogenic carcinoma in seven patients, TBC in four and bronchiectasis in one All patients were managed initially by the Eloesser procedure When the cavity was sterilized, as judged by serial cultures, a muscle transposition was performed to close the fistula and obliterate the pleural cavity

In total, 25 myoplasties were performed. The latissimus dorsi was employed in ten cases, the pectoralis major in eight, the serratus anterior in four, the pectoralis minor in two and the intercostal muscles in one. In four patients, a partial thoracoplasty was added No major complications or postoperative mortality occurred. Mean follow-up was 28·6 (range 11–60) months. There has been no recurrence of infection or fistula and the only late death was unrelated to BPF

It is concluded that this 'two-stage procedure', which includes initial thoracostomy and delayed intrathoracic muscle transposition, is a safe and effective treatment of chronic BPF associated with PE.

Carcinoma of the lung with chest wall involvement

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Of 868 patients operated on for lung cancer, 132 (15 per cent) presented with invasion of the chest wall on clinical and surgical criteria. Of these, 15 (14 per cent) were not resected. The average age of the patients was 64 (range 48–64) years. The male:female ratio was 10:1 The histologically predominant type was squamous cell cancer in 73 per cent of cases followed by adenocarcinoma in 17 per cent The surgical operations performed were 44 pneumonectomies, 11 bilobectomies and 56 lobectomies, all of them extended (to the chest wall on 36 occasions, to the pleura on 72 and, to the diaphragm on five)

The mortality rate was 12 patients (11 per cent), caused by respiratory insufficiency five times, by sepsis three times and in the rest by other causes. It was necessary to reoperate in 14 cases (12 per cent) eight thoracostomies, three clearings of the pleural cavity with pneumonectomies; on two occasions it was necessary to complete the pneumonectomy and on one occasion to make a secondary closure of the bronchial stump with a myoplasty procedure. The survival rate of the patients in this series was 68 per cent at 1 year, 49 per cent at 2 years and 21 per cent at 5 years. The prognosis is influenced by the tumour and ganglionic state and by the extent of pneumonectomy

Video-assisted thoracic surgery

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Videothoracoscopic techniques have been used over a 12-month period in 41 patients to perform 44 procedures. The applications of the procedure are diverse, the approach having been used diagnostically in 23 cases and therapeutically in 21. The diagnostic procedures included lung biopsy (11), intrapulmonary masses (nine) and pleural effusion (three), and were associated with a high diagnostic yield; accurate staging of lung cancer was possible, in particular nodal status in stage III disease This technique also allows assessment of the disease process in patients with malignant pleural effusion. The therapeutic procedures included pleurectomy and blebectomy (six), excision of emphysematous bulla (one), trauma (three), lung resection (five), pericardial window (one), ligation of patent ductus arteriosus (one), closure of bronchopleural fistula (one), drainage of empyema space (two), and repair of paraoesophageal hernia (one) These procedures were associated with minimal morbidity and a short hospital stay There were no intraoperative complications in either group and we did not have to revert to formal thoracotomy in any case This experience indicates an established and an expanding diverse role for video-assisted thoracic surgery

Recurrent pneumothorax: endoscopy *versus* open thoracotomy

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Endoscopic blebectomy (EB) is advocated as the treatment of choice for recurrent pneumothorax. A group of 28 consecutive patients who had received previous EB was compared with 157 patients who had undergone open thoracotomy (OT) to perform blebectomy during the previous 10 years

Both groups were comparable in age, sex, smoking habits and underlying pathology. Hospital stay, operative time, and recurrent morbidity and mortality were studied. Comparison was by means of Student's t test or χ^2 test as appropriate.

	EB	OT	*P*
Hospital stay (days)	4·5(2·3)	11(2·8)	0·05
Operating time (min)	31(9·9)	66(10·5)	0·05
Recurrence rate (%)	2	2	n.s.

Values are mean(s.d.). n.s., Not significant

In conclusion, endoscopic blebectomy has a shorter operative time and hospital stay. The difference in recurrence rate is not statistically significant.

Thoracoscopy in patients with thoracic trauma

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Experience proves that thoracoscopy is valuable for the diagnosis of organic injuries after severe thoracic trauma. Thoracoscopy was performed for exact diagnosis in 79 patients with severe thoracic trauma and the results analysed. A rigid thoracoscope and Storz procedure was performed with local anaesthesia, combined with neuroleptic analgesia The mean age was 35·6 years, and 72 were men Blunt thoracic trauma was found in 37 (47 per cent) and, of these, 31 (84 per cent) had lung injuries, ranging from single lesions to massive intrapulmonary haematoma and parenchymal damage Pneumothorax or haemothorax was diagnosed in 35 (95 per cent) of patients with blunt trauma

Penetrating trauma was found in 42 (53 per cent). The most common injuries were to the lungs – 39 (93 per cent) patients had haemorrhage and pneumohaemothorax of differing extents Diaphragmatic lesions were found in nine patients and lesions of the heart and pericardium in five.

In conclusion, thoracoscopy enables early and exact diagnosis of patients with severe thoracic trauma, as well as giving correct indications for operative treatment Complications after thoracoscopy were not observed.

Indications for major videothoracoscopic resection: lobectomy or pneumonectomy

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A series of 21 major pulmonary resections performed between October 1991 and November 1992 is reported. The series included two left pneumonectomies, 18 lobectomies and one segmentectomy This experience represents part of a large series of 157 thoracoscopic interventions performed in the same period

The criteria for major videothoracoscopic pulmonary operations were limited to three indications

1. Benign pulmonary diseases requiring lobectomy, e.g localized purulent bronchiectasis (four patients) and an arteriovenous fistula causing severe haemoptysis (one patient)
2. Endobronchial pulmonary metastases which were removable by classic wedge resection and therefore requiring lobectomy (two patients), when the primary extrapulmonary neoplastic site was under control.
3. Primary lung cancer at stage I ($T_1N_0M_x$) requiring lobectomy (12 patients). Lymphadenectomy was performed in each case In two cases pathology revealed stage II ($pT_1N_1M_x$) disease

Left pneumonectomy was performed videothoracoscopically in two cases of small tumour involving the distal end of the left main bronchus and not susceptible to sleeve lobectomy

There were neither major operative complications nor any deaths. Five further patients intended to undergo videothoracoscopic resection were converted to open procedure because of intraoperative technical problems.

Evaluation of extended mediastinal lymphadenectomy in 5-year survival of patients undergoing resection for bronchial carcinoma

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In the 3-year period 1985 to 1987, a randomized study was performed on 288 lung resections carried out for non-small cell pulmonary carcinoma. Alternate patients were operated on conventionally with local lymphatic resection, or received in addition extended mediastinal lymphadenectomy. Of the patients undergoing conventional surgery, two died (1·6 per cent). In this group 43 pulmonectomies and 81 lobectomies were performed. Of the group undergoing extended lymphadenectomy, three patients died (2·5 per cent); in this group there were 46 pulmonectomies and 76 lobectomies There was no significant difference in the 5-year survival rate between the two groups In cases of squamous cell carcinoma, the 5-year survival rates were 58 and 42 per cent, in favour of extended mediastinal dissection. Considering stages II and IIIA lymph node-positive squamous cell carcinoma, the 5-year survival rates were 40 and 26 per cent in favour of extended mediastinal lymphadenectomy. In adenocarcinoma the 5-year survival rates of N_1 and N_2 patients were 34 and 22 per cent; here too extended lymphadenectomy was better In large cell carcinoma the rates were 30 and 20 per cent.

On the basis of these data, lymph node sampling is performed from the upper mediastinum, the subcarinal region and the pulmonary ligament. If the cytological results are positive, extended mediastinal lymphadenectomy is performed

Operative treatment of erythrophobia

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The morbid flush of the face is a most disturbing condition in adults Curative measures are inadequate. Considering erythrophobia as an organic disturbance, in 1985 systematic treatment by thoracoscopic sympathectomy under local anaesthesia was started. The sympathetic trunk was divided in thoracic segments 2, 3 and 4 on both sides over a period of 2–3 days. In all, 47 patients have undergone operation Of these, 43 were followed: 24 men and 19 women, aged from 18 to 54 years.

The results have been established by a postoperative check between 1 and 8 years However, 67 per cent (29 patients) were checked 5–8 years after transpleural neurotomy (TPN). Excellents results (no blush at all) were attained in 32 patients (74 per cent), good results (rare blush in situations of high mental tension) was seen in five patients (12 per cent) and satisfactory improvement (occasional blush, but without causing psychological problems) occurred in three (7 per cent). Relapses after 1–3 years occurred in three patients (7 per cent) These were corrected by successful reoperation. In conclusion, thoracoscopic sympathectomy is a valuable procedure to cure erythrophobia.

Training

Quo vadis, chirurgia?

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In 1982, long before the worldwide advent of the era of laparoscopic surgery, James D. Hardy, famous for the first lung transplantation (1963), asked the question. 'Will the general surgeon become extinct?' and suggested that among threatened species this one was worth saving. He drew attention to the danger of overspecialization, but the recent desirable spread of minimally invasive surgery is not an interdisciplinary, but more an intradisciplinary, problem The benefits are counterbalanced by many drawbacks, the largest of which is believed to be the inefficient training of young surgeons in open abdominal surgery Even before the advent of laparoscopic surgery the education of young surgeons became unsettled. partial gastrectomy was first to disappear, then vagotomy became rare, followed by choledochotomy If surgeons are undertrained how will they safely convert a laparoscopic procedure to an open one?

The new era of laparoscopic intervention opens up new vistas, but the light is linked with shadow Repeated references in Presidential Addresses on both sides of the Atlantic warn about problems with surgical training and it is an obligation of us all, the large surgical associations and the leading national surgical boards, to prepare an effective and long-term strategy for a solution to this problem

Demands on surgeons in Spain

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Demands and legal procedures are rising drastically in Spain for surgeons To ascertain the main causes for this, a study has been performed which is based on surgeons' experience and the registry of the National Health System (NHS)

First, a study of the register of demands on surgeons located in the NHS in public practice since 1978 was carried out Second, a questionnaire with 14 specific questions (the same items that were the cause of demands to the NHS) was sent to 13 026 surgeons all over Spain (13 surgical specialities) The questionnaire had nine open and fifteen closed questions. Of the 13 026, 900 were sent to private practitioners

Both sets of data were analysed and compared The main causes in the NHS register were surgical delay (26·6 per cent), inappropriate follow-up (25·0 per cent) and unclear indications (21·1 per cent)

The data obtained show a similarity between public and private practice. Up to now, although demands for surgical omissions or malpractice are increasing, these are not the main causes in our country.

Comparative interspecialty operative audit

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All operative cases during normal working hours and 'out of hours' over 1 year were subjected to a detailed retrospective comparative audit 'Working day' cases were defined as those operated on between 09.00 and 17 00 hours Monday to Friday and 'out of hours' cases as those between 17.00 and 09.00 hours during weekdays and 24 h per day during weekends and bank holidays All hospital operating specialties were reviewed. The number of cases taken to theatre was the caseload. Workload was calculated from the British United Provident Association (BUPA) schedule of procedures with allocation of intermediate equivalent values to each case. Timeload was calculated using the Voluntary Health Insurance Schedule of Procedures Interspecialty caseload, workload and timeload results are shown.

It is concluded that orthopaedic surgeons have the greatest caseload and timeload. Specific guidelines for orthopaedic workload are required Orthopaedic surgeons failed to have the greatest workload due to biases inherent in the BUPA scales, which favour general surgical operations with more detailed listing of grades. No account is taken for extra time required at orthopaedic operations.

Specialty	Caseload	Workload	Timeload
Orthopaedic	2525 (40)	1905 (31)	2481 (34)
General surgery	1588 (25)	1999 (33)	1729 (24)
Obstetrics and gynaecology	795 (12)	795 (13)	961 (13)
Ear, nose and throat	1096 (17)	707 (11)	663 (9)
Ophthalmology	402 (6)	746 (12)	1470 (20)
Total	6406 (100)	6152 (100)	7304 (100)

Value in parentheses are percentages

Meeting the standards for surgical training

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A 1-year retrospective audit of operative workload for surgical trainees to assess their operative exposure is presented. Operative caseload was recorded from the theatre logbooks for each consultant, registrar and senior house officer (SHO) within each specialty. Using the 1985 Wallace formula, service equivalent values (SEVs) were assigned to all surgical teams, where consultant = 1·0, registrar = 0·7 and SHO = 0·5 The workload and timeload for each grade were calculated using intermediate equivalent values (IEVs) as recommended by the British United Provident Association schedule of procedures and the Voluntary Health Insurance time scale values, respectively. Consultants undertook a mean of 55 per cent of the total operative workload, registrars 42 per cent and SHOs 3 per cent only The table shows the results for the orthopaedic specialty

	Consultant	Registrar	SHO
No. of cases	448 (55)	330 (41)	32 (4)
Workload (IEV)	428 (67)	206 (33)	1 (0)
Timeload (h)	557 (68)	253 (31)	8 (1)

Values in parentheses are percentages

Based on the Royal College of Surgeons of England 1990 recommendations for a standard general surgical team in a firm comprising one consultant, registrar and SHO (SEV 2·2), the consultant should do 45 per cent, registrar 32 per cent and SHO 23 per cent of the total workload It is concluded that the operative workload of SHOs must be increased Registrar operative workload was adequate, but was biased towards trauma Theatre logbooks should include information to assess surgical training and workload.

Scalpel-fax: the first customized hypermedia manual for surgical quality control and training

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An educational–learning–training tool for operative surgery has been designed to satisfy the needs of a range of medical personnel from consultant surgeon to scrub nurse, from administrator to surgical equipment manufacturer For day-to-day surgery, for teaching. for reference and for quality assurance, Scalpel-fax is a user-friendly combination of well founded surgical expertise, established through years of experience, and software technology Operations (currently numbering 60) are structured in the form of concise, integral steps consisting of procedures and decisions, and are stored as ordinary text files in any word processor format. When a particular operation is selected using Scalpel-fax the corresponding file is loaded into the application and automatically converted into hypertext, each operation step being shown as a single

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numbered card on the screen. Operations are therefore featured one step at a time, and are followed algorithmically. In this manner the user emulates a complete operation, from checking the equipment inventory to filling in a postoperation surgical report Scalpel-fax can be customized The user is able to easily modify both text and hypertext to comply with his or her own regimen No prior computer knowledge is necessary. Written in Smalltalk/v windows for use on personal computers, Scalpel-fax currently offers four main hypertext facilities: revealing explanatory notes, skipping irrelevant steps, switching operations and displaying colour diagrams and pictures Navigation of the interface is facilitated by clicking hypertext, icons and buttons with a 'mouse' Further developments will incorporate CD-ROM, sound, video and multimedia

Transplantation

Quantitative analysis of structural and ultrastructural ischaemic changes following preservation of rat liver in University of Wisconsin–Belzer and Ringer's solutions

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Morphological consequences of organ preservation on hepatocytes and subcellular organelles because of altered metabolism and gradual energy depletion have been quantified sequentially.

Rat livers from 60 male Lewis rats weighing 200–250 g were stored at 4°C in University of Wisconsin (UW)–Belzer and Ringer's solutions following initial perfusion. Biopsies were performed immediately after flushing and 6 h, 12 h, 24 h and 36 h after cold storage for histological and ultrastructural examinations The cellular and nuclear areas of the hepatocytes were determined using light microscopic specimens, while the extent of subcellular organelles was quantified stereologically on electron microscopic photographs (×24 000) .

Over a period of up to 36 h the size of the hepatocytes increased steadily by 20 per cent with Ringer's solution, while a reduction of 10 per cent was noted with UW–Belzer. The mean(s d) nuclear area remained unchanged at 42(5) µm^2 with UW–Belzer, while with Ringer's there was considerable swelling of up to 63(7) µm^2. This leads to significant alterations in the cytoplasmic–nuclear ratio for both solutions The cytoplasmic matrix increased by 30 per cent with Ringer's while with UW–Belzer it decreased by 20 per cent after 36 h. Steady mitochondrial swelling from 0·7 µm^2 after flushing to 1·1 µm^2 after 36 h was noted with Ringer's There was no initial (6 h, 12 h, 24 h) significant change in mitochondrial size with UW–Belzer; only after 36 h was a slight swelling to 0·8 µm^2 apparent The smooth endoplasmic reticulum showed an intense vacuolization with Ringer's; after 36 h, 9 per cent by volume of the hepatocyte count consisted of vacuolized smooth endoplasmic reticulum. In contrast to Ringer's, only 0·5 per cent by volume of the hepatocyte count in UW–Belzer was made up of vacuolized smooth endoplasmic reticulum. For both solutions there was lysosome activation, which was more substantial for UW–Belzer (7 per cent by volume after 36 h) than for Ringer's (3 per cent by volume after 36 h) Peroxisomes and Golgi complexes showed no alterations

Hypothermic ischaemia leads to cellular and subcellular alterations in the supravital liver, which are far more substantial in the case of Ringer's solution Quantitative morphological examinations seem to be appropriate in establishing assured correlations between cellular structure and function in the ischaemia–reperfusion damage within the scope of liver transplantation.

Reduction of venovenous bypass in the anhepatic phase of liver transplantation using the piggy-back technique

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Some patients do not tolerate vascular clamping during the anhepatic phase of liver transplantation and a venovenous bypass is required for haemodynamic stability Another possibility is the piggy-back technique with preservation of the inferior vena cava. The author's experience with this technique is described.

In the past 4 years, 92 adult patients underwent orthotopic liver transplantation· 31 patients with venovenous bypass, 23 without bypass and 38 with the piggy-back technique. This technique was introduced in June 1991.

Before the use of the piggy-back technique, venovenous bypass was used in 60 per cent of patients, however, bypass is necessary in only 12 per cent of cases. The length of operation and the blood transfusion requirements were significantly reduced with the piggy-back technique.

This experience indicates that the piggy-back technique decreases the need for venovenous bypass, reducing the operating time and blood transfusion.

Family liver transplantation in children: improvement in surgical technique

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In the past 4 years liver transplantation has been managed by cooperation between three universities. For paediatric liver transplantation this management was successful in the following areas· collection of liver specimens, preoperative staging in children, the use of a common transplantation team, and improvement of postoperative therapy Complications and costs were thus significantly decreased

Liver transplantations were performed primarily for biliary atresia and metabolic liver diseases Liver transplantations were undertaken in 60 children using full size, split liver and a segmental technique A further two children underwent family liver transplantation (FLT), with parents the donors for left liver segments II/III Preoperative treatments, transplantation procedure and postoperative treatment were performed in cooperation with other European centres. Of 62 children, five died over a 4-year period In eight children a retransplantation had to be performed

A combined Euro-children liver transplantation team was. for safety and economic reasons, the recommended management The authors believe that in future liver transplantation in children will be by FLT using the laser, the Cusa and intraoperative duplex ultrasonography.

Orthotopic liver transplantation in the pig: the 27 first cases

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The first 27 cases of orthotopic liver transplantation in the pig, in which 55 animals were used, are analysed The first 19 transplants were performed with passive venovenous portojugular shunt; in the last eight an active portocaval jugular shunt with a Biomedical pump was used

Anaesthetic and surgical techniques emphasized the inherent problems to the animal's survival, water and electrolyte balance, transfusion support, organ harvesting, recipient operation, as well as anaesthetic and surgical complications during and after surgery

The outcome of the series was. two deaths during surgery, nine deaths in the first 6 h, eight deaths from 6 to 24 h, two deaths from 24 to 48 h and six pigs survived 48 h after surgery

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Liver transplantation in patients with previous portocaval shunt

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A total of 12 liver transplantations in patients with portasystemic shunts, either portacaval or distal splenorenal in one patient, have been performed in the past 2 years Orthotopic liver transplantation (OLT) was indicated for severe liver failure caused by hepatitis C postnecrotic liver cirrhosis in seven cases, hepatitis B virus liver cirrhosis in one, multifocal hepatocellular carcinoma in one, cryptogenetic liver cirrhosis with acute thrombosis of the portacaval shunt and liver failure in one, and alcoholic cirrhosis in two The mean interval between portacaval shunt and OLT was 78 (range 2–192) months. In nine cases, the piggy-back technique was used. A venovenous bypass was employed in the first case as well as when there was acute thrombosis of the portacaval shunt The portasystemic shunt made hepatectomy easier because of the absence of portal hypertension During dismantelling of the portacaval shunt, splanchnic congestion was noted, necessitating closure of the abdominal wall with a prosthetic mesh in one case The mean packed red cell transfusion was 11·3 units Transplantation in the patient with a thrombosed portacaval shunt was technically difficult, severe portal hypertension requiring a packed red cell transfusion of 51 units. There was no postoperative mortality. The clinical course was uneventful in eight cases. One patient presented with hyperacute rejection related to positive cross-match and had to be retransplanted The mean hospital stay was 35·9 (range 12–117) days. After a mean follow-up of 13·7 (range 7–23) months two patients died from recurrent viral hepatitis at 11 and 23 months respectively

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The presence of a patent portasystemic shunt, whether central or selective, is not a contraindication to OLT and the authors are persuaded that the piggy-back technique is particularly useful in these cases.

Transplant nephrectomy: factors influencing morbidity and mortality

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Of 1048 renal transplants performed between 1971 and 1990, transplant nephrectomies were performed in 86 recipients (8·2 per cent). Mean patient age was 33 (range 3·8–66 5) years. Postoperative complications occurred in 51 patients (59 per cent). The number and severity of complications were greater in patients with acute rejection. Four patients died: one from bowel ischaemia, two from disseminated intravascular coagulation and one from pulmonary embolism. The external iliac artery was ligated to control haemorrhage in four patients. The nephrectomy rate rose significantly ($P <$ 0 005) when cyclosporin A was initially introduced

Transplant nephrectomy is a hazardous operation. Most failed grafts can be left *in situ* without compromising patient well-being The introduction of new immunosuppressive regimens may temporarily increase indications for transplant nephrectomy.

Familial amyloidotic polyneuropathy: a new indication for orthotopic liver transplantation

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The objective of this paper is to present the long-term results of seven patients undergoing orthotopic liver transplantation (OLT) with a diagnosis of familial amyloidotic polyneuropathy (FAP) The FAP diagnosis was based in all cases on: (1) compatible neurological symptoms and electromyography, (2) family history, (3) location of amyloid in abdominal fat and sural nerve; and (4) presence of a biochemical marker of the disease in serum. The mean follow-up was 6·4 (range 4–18) months and the patient survival rate 100 per cent.

Results of the investigations showed that: (1) the biochemical marker of the disease disappeared from plasma in all cases; (2) the neurological situation was discretely improved in the two patients who had received a transplant more than 10 months previously, and (3) electromyography neither improved nor worsened in any of the cases

In conclusion, it is believed that, while a less aggressive solution is awaited, a liver transplant may be useful in the treatment of certain patients with FAP to halt the neurological deterioration of the disease.

Facultative sequential immunosuppression in renal transplantation

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Cyclosporin toxicity can impair the results of renal transplantation. The use of a facultative sequential immunosuppression regimen may help to avoid this phenomenon.

Such a regimen used in a district general hospital has been prospectively reviewed At surgery the recipient receives 500 mg methylprednisolone and then cyclosporin depending on the urine output (UO) at 6 h If UO >250 ml, the patient is given cyclosporin 10 mg kg^{-1} day^{-1} orally plus prednisolone 10 mg day^{-1} orally. If UO <250 ml, the patient is given azathioprine 2 mg kg^{-1} day^{-1} orally plus prednisolone 30 mg day^{-1} orally. When UO >500 ml, cyclosporin 2 mg kg^{-1} day^{-1} orally is added and later increased as the urinary creatinine level falls

Over a 6-year period from 1986, 165 cadaveric renal transplants have been performed using the above regimen for recipient immunosuppression The cumulative 1- and 5-year graft survival rates are 92 and 84 per cent respectively. The cumulative 1- and 5-year patient survival rates are 94 and 86 per cent

In conclusion, the above protocol has been shown to be an effective method of immunosuppression, avoiding the problem of cyclosporin nephrotoxicity while the graft recovers from preservation damage.

Trauma

Injuries and their management in Australian aboriginals

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The Australian aboriginals are not war-like. If they came originally from somewhere in south central Asia and migrated south-east across interconnecting land masses, they may have been escaping from more belligerent races There was never any large armed resistance to white settlement. When small tribes resisted they were easily overcome, particularly because of the dominance of white firearms. Within Australia there was little major intertribal fighting and most of it for protection of tribal areas Most fighting was personal and frequently related to insults or arguments relating to women.

The management of injuries in the Australian aboriginals is discussed The aboriginal medicine man was a man of high degree. He had specific training. His work was involved mainly in illnesses and problems of the mind The actual management of injuries was most often carried out by tribal elders. The work of the medicine man and the methods of management of injuries are discussed

Cervical spine injury in patients with facial fractures

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A prospective 1-year study was undertaken to document the incidence of concomitant fracture of the cervical spine with facial trauma A total of 582 consecutive patients with facial fractures referred to the National Referral Centre at St James's Hospital (from 1 January 1992 to 31 December 92) were included in the study Some 1 04 per cent (n = 6) of patients with facial fractures were found to have associated cervical spine injury All of the cervical injuries occurred in the subgroup of patients with facial trauma following road traffic accidents (n = 94), resulting in an incidence in this subgroup of 6 per cent. Five of the six patients had associated multiple injuries. All six had facial lacerations and five had mandibular fractures Each of the six patients complained of either neck stiffness or pain Only two of the six cervical fractures (two patients with fractures of C2) were observed on standard three-view plain cervical radiographs. Four of the fractures were seen on computed tomography (CT): the two patients with fractures of C2 and two patients, one with compression fracture of the vertebral body of C4 and the other with comminuted fracture of the vertebral body of C7 Two patients had fractures that were diagnosable only on stress views under radiographic screening (subluxation of C4/C5 and subluxation of C5/C6).

This study illustrates the need for a high index of suspicion of associated cervical injury in patients with facial fractures, especially after high velocity type injury It also illustrates that negative plain radiographs may require further radiographic investigation (CT or stress views) and it exposes the limitations of CT in the diagnosis of ligamentous injury of the cervical spine in which stress views under radiographic screening of the spine are of value.

Abdominal trauma

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Unrecognized abdominal injury remains a frequent cause of preventable death. In penetrating trauma the diagnosis may be very clear when there is obvious damage to the abdominal wall and bowel is protruding Penetrating trauma to the chest, back, buttocks and perineum should also arouse suspicion that the peritoneal cavity has been breached. In gunshot wounds mandatory exploration is the preferred approach for diagnosis In stab wounds without other clear physical findings the wound is explored under local anaesthesia In cases of fascia penetration, peritoneal lavage is helpful.

In blunt trauma, the peritoneal signs are often subtle, overshadowed by pain from associated injury and masked by head trauma or intoxicants. Diagnostic peritoneal lavage remains the cornerstone of triage in patients with life-threatening blunt abdominal trauma. Routine ancillary tests for potentially occult injuries include nasogastric tube placement for ruptures of the left diaphragm, Gastrografin contrast study for duodenum perforation and pyelography for urological injury Ultrasonography may become a valuable tool in the initial assessment of the injured abdomen. Computed tomography is useful as a complementary diagnostic tool in selected patients and is the critical test for guidance of non-operative management of known intraperitoneal trauma

Ultimately, the most important principle in the management of blunt abdominal trauma is repeat physical examination by an experienced surgeon

Surgical treatment of brain injuries caused by firearms

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A total of 1401 patients have been examined in the University Clinical Centre in the period from the beginning of war in 1991 until 1 November 1992. In all, 1095 patients were admitted to the Emergency Centre and 139 of these were treated in the Neurosurgical Department. The age of the patients ranged from 18 to 76 years. Death occurred in 67 (48 per cent) patients Most of the patients (114) were aged between 18 and 40 years A Glasgow Coma Score (GCS) < 8 was seen in 78 patients, of whom 23 (30 per cent) survived. The group of patients with GCS ⩾ 8 comprised 61 patients, with a survival rate of 82 per cent (11 patients died).

The best prognosis may be given to the cases with tangential skull injuries (of 17 cases only two died).

Intracranial pressure monitoring in critically ill patients

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Implantation of an intracranial epidural pressure sensor in patients with presumed increase in intracranial pressure (ICP) can be performed for documentation purposes to aid in treatment, and for monitoring of therapy

During the past 5 years, ICP monitoring was performed in 65 traumatized patients, and in 11 patients after liver transplantation After complete neurological evaluation and cranial computed tomography, the sensor was implanted under sterile conditions on the intensive care unit. Two types of sensor and monitoring system were used; each was studied for practicability of implantation and long-term monitoring as well as for reproducibility of results and correlation of ICP with clinical parameters

The procedure took ⩽ 35 (mean 23) min for completion. Complications were minimal. No infection was documented, but in one patient with acute hepatic failure intraoperative bleeding from the site of the sensor eventually led to its removal In 26 patients, increased ICP was found that did not correlate with clinical parameters, this led to therapeutic consequences (hyperventilation, barbiturate use, diuresis, osmodiuresis) In spite of modification of surgical technique and the use of other monitoring systems, in 19 patients increased ICP as recorded by the present system did not meet clinical standards or could not be reliably reproduced.

As a result, the use of a single system in the authors' institution was agreed, and the technique of implantation and monitoring standardized such that regular interdisciplinary training of all personnel involved can be performed This has led to reliable ICP monitoring over the past 14 months

Injuries of the small and large intestine

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A total of 261 patient were treated for injury to the small and large intestines. Most were young people aged 20–40 years The main reason for injuries were knife and crash wounds Overall, 175 patients had injured

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small intestine, 92 penetrating and 83 blunt injuries. The jejunum was injured in two-thirds of cases. The stomach was injured in 47 patients After primary repair a special tube for enterodecompression was used Mortality rate from injuries of small intestines was 11·4 per cent With injuries of the large intestine were 86 patients. In one-third of cases the transverse colon was injured, less commonly the sigmoid or ascending colon In all, 167 patients (64 per cent) with damaged small and large intestine underwent primary repair, 27 (10 per cent) had resection and anastomosis, two had resection and exteriorization, 37 (14 per cent) resection with ileostomy or colostomy and 30 (11 per cent) only ileostomy or colostomy. Morbidity and mortality rates correlated with the severity of associated injuries and also the time interval between accident and operative treatment The most frequent complication was suppuration of the wound. Thirty-five patients died, a mortality rate of 13 4 per cent. The most frequent cause of death was peritonitis or shock

Unreamed nailing technique in compound tibial fractures: a comparison with external fixation

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This study aimed to determine the efficacy of an unreamed nailing technique compared with external fixation in open tibial shaft fractures. Between 1986 and 1992, 204 compound fractures of the tibial shaft were treated by either unreamed nailing or external fixation. Since June 1992 an unreamed titanium nail has been additionally implanted. In total, 165 fractures underwent external fixation, 22 were stabilized with the unreamed nail and 14 were treated by reamed nailing. Three fractures were managed conservatively

Of the fractures treated, 192 healed Three IIIC fractures required subsequent amputation. A deep bony infection was observed in seven cases (3 4 per cent); 35 received autogenous cancellous bone grafts. In three cases a transport corticotomy was performed owing to large bony defects. In 17 cases the procedure was changed: cases with external fixators were changed to plates in eight patients, to unreamed nails in two, and to reamed nails in four The unreamed nail was changed to a reamed nail in three patients due to either a varus or a valgus deformity. Breakage of the locking bolts occurred four times in regular unreamed nails. There was no effect on the bony consolidation

In distinction to the external fixator the unreamed nail is more comfortable for the patient. In addition there is no increased risk of infection, although the regular unreamed nail is a less stable implant that might require a change to a reamed nail after consolidation of the soft tissue The titanium unreamed nail offers more stability with primary fracture healing.

Mesenteric and bowel injuries after blunt abdominal trauma

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This study aimed to analyse the distribution and severity of the lesions, the types of accident and the diagnostic and therapeutic aspects of patients with mesenteric or bowel injuries after blunt abdominal trauma. Twenty male and four female patients (mean age 39 years) were victims of 17 vehicle crashes (16 car occupants and one motorcyclist) and seven direct abdominal impacts in civilian life Twelve victims of car accidents were under 40 years of age. Fourteen patients occupied the driver's position and eight used a seat-belt

Thirteen patients developed hypotension and shock after injury. The average time between the accident and surgical exploration was 39 h The findings were 14 small bowel perforations, seven colonic perforations and 15 mesenteric ruptures. Twelve patients had an associated abdominal injury: six hepatic, five splenic and five pancreatic Fourteen patients had an associated thoracic injury

Nine small bowel resections, eight intestinal suturings and one Hartmann's operation were carried out There were two deaths (8·3 per cent) and 13 surviving patients had postoperative complications (59 per cent). Mean hospital stay was 24 days

In conclusion, the use of a seat-belt and the type of accident were not related to the type of abdominal injury. However, morbidity and mortality were closely related to the existence of an associated abdominal or thoracic injury.

GEMIS: a new acronym for polytrauma illness

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Multiple and sequential organ failure after trauma or major surgery was described in the mid-1970s Up to now, denomination of this syndrome has been based on clinical signs and symptoms appearing only at the end stage of the illness. Manifestations of multiple organ failure (MOF) are the end result of anatomopathological damage produced by deregulation and loss of many homoeostatic and self-protecting mechanisms of the body, which are activated in an abnormal way by hypo-oxygenation, tissue disruption and necrosis

Oedema is the first step in such pathological change, and it arises from microcirculatory damage. Studies performed by the authors with multiple trauma patients demonstrated that oedema occurs in different organs at the same time, instead of taking place in one organ after another in a step-by-step pattern, as assumed by other workers. Specimens of tissues and organs were taken at different times after the primary event. All tissues examined by light microscopy showed signs of inflammation and oedema shortly after trauma This is consistent with the hypothesis that microcirculatory damage arises immediately after major trauma, is widely and simultaneously distributed in all body tissues, and shows its effects in various organs at different times only because of dissimilar functional reserves of each organ The main pathological event in MOF, therefore, is the structural and functional damage to the microcirculation.

MOF, MSOF (multiple system organ failure) and multiple organ dysfunction are therefore incomplete names for the syndrome, because they refer only to late clinical events A new acronym has been coined – GEMIS (generalized endothelial microcirculation injury syndrome), highlighting the common early pathological event (generalized endothelial damage) present, even if latently, from the beginning in patients developing MOF Therefore acute respiratory distress syndrome, hepatic, renal, intestinal, cardiac and cerebral failures have to be considered as 'symptoms' of GEMIS instead of distinct clinical syndromes. Respiratory function is always the first to fail, because of the delicate alveolar capillary structure.

Haemorrhage from pelvic fracture

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Haemorrhage is the leading cause of mortality in patients with pelvic fracture The pelvis provides a large 'hidden' space into which haemorrhage can occur. To date there has been no reported correlation between pelvic fracture displacement and pelvic volume However, anecdote suggests that a small displacement leads to a relatively large increase in pelvic volume. Ten skeleton pelves were sealed with elastic membranes, and the volume of the true pelvis measured by filling a polythene balloon with water. Fixed-width blocks of progressive 1-cm increments were inserted at the pubic symphysis to simulate diastasis, and the volume measurements repeated. Further groups of measurements were made to simulate both disruption at the sacroiliac joints, and combined separations of both the symphysis and sacroiliac joints. For each 1-cm widening at the pubic symphysis there is a 4·6 per cent increase in the volume of the true pelvis; for each 1-cm displacement at the sacroiliac joint there is a 3·1 per cent increase.

These results demonstrate that a wildly displaced fracture that, for example, widens the symphysis by 10 cm and opens a sacroiliac joint by 3 cm, increases the pelvic volume by only 55 per cent. There is therefore a relatively small increase in pelvic volume with fracture displacement The increase in blood loss is accounted for by the associated soft tissue damage to the pelvis, which occurs during maximal displacement at the time of injury Haemorrhage occurs both into the pelvis and through the disrupted soft tissue envelope, out of the pelvis. Restoration of bony stability is therefore important for stabilization of the soft tissues to allow tamponade and clotting, and to prevent subsequent clot displacement External fixation of the acutely injured pelvis does have the effect of reducing pelvic volume but, probably more importantly, it helps the pelvic basin to stop leaking.

Operative treatment of fracture of the os calcis

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A prospective study of 24 patients with displaced intra-articular fractures of the os calcis was performed to compare operative with non-operative management of these problematic injuries. Twelve patients underwent internal fixation of the calcaneus followed by early mobilization and 12 were managed non-operatively, also with early mobilization. All patients were reviewed 15 months later using eight parameters to assess outcome.

Of the 12 patients who had internal fixation, eight had returned to work. Pain-free ambulation distance was significantly longer (mean 4 km) in this group and only one patient complained of footwear problems, a unilateral change in shoe size. Of the 12 patients who were managed conservatively, only three had returned to work and eight had a unilateral increase in shoe size, while the mean pain-free walking distance in this group was only 1 km. The mean range of subtalar movement was 24° in the operated group but only 12° in the conservatively treated group ($P < 0{\cdot}05$). Radiological follow-up demonstrated partial or full restoration of Bohler's angle in the patients who underwent internal fixation. Plating of calcaneal fractures through a lateral approach for optimal results is recommended when managing displaced intra-articular fractures in patients under 40 years old.

Ankle ligament tears in sport: the role of magnetic resonance imaging

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The purpose of this study was to ascertain the precise benefits of magnetic resonance imaging (MRI) in lateral ankle ligament tears and to establish whether this method bears any advantage over conventional diagnostic modalities when assessing these injuries. A total of 54 patients, all of whom had acute lateral ligament tears with positive stress radiographs, were reviewed by an orthopaedic surgeon. All patients then underwent a technetium isotope scan to screen for the presence of osteochondral fractures or additional soft tissue injury. Patients demonstrating marked uptake of isotope were further assessed using ankle MRI. Of 54 bone scans, 17 were normal and 16 showed minimal isotope uptake. The remaining 21 had increased uptake which suggested post-traumatic synovitis in 16 and deltoid ligament injury in 12. MR images in these 21 individuals confirmed anatomical lateral ligament tears in only seven patients, and deltoid ligament tears in nine. MRI detected otherwise undetected joint effusions in four patients. There were five osteochondral fractures in the whole series (three talus, one lateral and one medial malleolus), all of which were suggested on bone scan, but only three of which were shown on MRI.

We recommend screening with plain stress radiographs and scintigraphy to improve diagnostic accuracy in ankle ligament injuries and propose that MRI be reserved for patients whose radiograph or bone scan suggests a more severe injury or fracture.

Scene or emergency room thoracotomy for patients with severe trauma

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Resuscitative thoracotomy (RT) for trauma is only occasionally successful. In previous reports RT has been delayed by the time for transfer from the scene to the emergency department. In the London area the Helicopter Emergency Medical Service (HEMS) provides early medical attention at the scene, so widening the scope of field resuscitation procedures available; this has included RT for severe and blunt trauma.

During the period from 1990 to 1991, RT was performed by non-thoracic surgeons on 16 patients (15 men and one woman of median (range) age 25 (9–38) years) from a total of 1084 HEMS missions. Nine procedures were performed at the scene and seven in the casualty department. Medical attention was administered a median(s.i.r.) 16·2(4·0) min from the initial call to the ambulance service. The median(s.i.r.) Injury Severity Score was 29·9(11·8) for all patients and was not statistically different between patients having RT at the scene or in casualty. The time spent at the scene was significantly greater for those patients undergoing RT (35·1 *versus* 16·2 min, $P < 0{\cdot}01$). No patient survived RT but temporary improvements occurred more frequently in patients with penetrating injuries.

These results demonstrate that RT has limited efficacy and lend support to the concept that a 'swoop and scoop' policy should be adopted for patients at the scene after initial simple resuscitation techniques have been implemented. Thoracic surgical expertise should be sought early in the management of these patients when they arrive in the casualty department.

Hepatic injuries

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From January 1984 to December 1990, 1326 injured patients were admitted. The most frequent cause of admission was head injury. Some 265 (20·0 per cent) needed surgical treatment and 164 (12·4 per cent) underwent emergency laparotomy. Of these 164 patients, 57 (34·8 per cent) had liver injuries, 47 of whom were male with a mean age of 32 years. The most common cause of hepatic injury was motor vehicle accident (43), and 49 patients suffered from blunt trauma. Peritoneal lavage is the best diagnostic method. A total of 23 patients had hypovolaemic shock in the emergency department. Hepatic injuries were frequently associated with injuries in others areas of the body, such as the thorax (28) and head (23).

All patients had laparotomy. Some 62 lesions were found in 57 patients. The right lobe was more frequently injured, especially segments VI–VII. A total of 65 per cent had Moore grades I–IV. Liver injuries were frequently associated with other lesions, for instance retroperitoneal haematoma (14) and splenic injury (12). Of the 62 lesions, 57 were treated conservatively: 43 had hepatic sutures, seven haemostasis (direct compression, electrocautery or haemostatic substances) and seven no procedure. Partial hepatectomy was performed in five patients, of whom three also needed gauze packing to control bleeding. Twenty-seven patients were admitted to the intensive care unit after operation. Eight patients suffered complications. Reoperation was rare – six cases plus three to remove hepatic packing. The mortality rate was 9 per cent (five patients, two of whom died during surgery).

Motor vehicle accident is the major cause of injury. Liver trauma is the most common intra-abdominal injury in multiple trauma patients. Resection surgery is rarely required. Mortality and morbidity rates are low.

Management of isolated large bowel gunshot injuries

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This retrospective study reports the treatment of 384 unselected patients with isolated large bowel or large and small bowel gunshot injuries (56 per cent of the total number of patients with large bowel injuries). Rectal injuries have been excluded from this study. Most of the wounds were in the ascending colon (116 cases) and transverse colon (122 cases).

The surgical technique chosen depended on the general condition of the patient and the size and severity of the damage. Bowel injuries with a diameter of < 2 cm with intact mesenteric blood supply (27 cases) were sutured. The wound was sutured followed by exteriorization of the bowel in 76 cases, extraperitonealization in 47 cases and proximal colostomy in 106 cases. The bowel was exteriorized in 50 cases.

Resection was indicated for major wounds, multiple injuries in a segment, partial or total rupture of the bowel and mesenteric injuries. Ascending hemicolectomy was performed in five cases and ascending colon resection with colostomy and ileotransverse anastomosis in 23 cases. Transverse colon resection with proximal and distal colostomy was performed in nine cases and with total proximal colostomy in 41 cases. The mortality rate was 30·5 per cent.

A systematic approach to the surgical treatment of traumatic enophthalmos

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Enophthalmos describes the backward displacement of the globe owing to traumatic disruption of the bony orbit. It leads to diplopia and cosmetic defect. The surgical treatment of enophthalmos has historically been empirical and unpredictable. This paper describes a systematic approach for the management of traumatic enophthalmos. Enophthalmos is measured before operation using an exophthalmometer The orbital volume is assessed radiologically using a low-dose computed tomographic scanning technique, utilizing 10 per cent of the conventional radiation dose. The surgeon can therefore identify before operation the implosion sites and quantify volume changes Bone grafts are harvested by a trephine technique from the iliac crest, and can then be modelled to the appropriate volume and shape using a purpose-built steel bone press This systematic approach has been used in ten cases with satisfactory results in nine.

Traumatic hip dislocation

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Between January 1990 and April 1992, 13 patients with traumatic hip dislocation were treated in the authors' surgical department. In two cases, dislocation of the hip occurred alone, without any bony injury. In two other cases, the hip dislocation was accompanied by fracture of the upper femur. In three of the 13 patients, Pipkin dislocation fractures were seen, while in six the traumatic hip dislocation was combined with fracture of the acetabulum. Traumatic hip dislocation is an injury that affects almost exclusively younger patients

Follow-up was carried out in seven patients Clinical examination included radiography and sonographic procedures Patients in whom no metal had been implanted had additional magnetic resonance imaging (MRI) studies A large variation was seen in the amount of periarticular calcification. MRI revealed no damage to the cartilage in patients with pure dislocation The overall range of motion at follow-up was 64–100 per cent, compared with the healthy side

When treating traumatic hip dislocation we emphasize the importance of physiotherapy and early mobilization without weight-bearing within 12 weeks of trauma The best results were seen in patients with a pure hip dislocation without associated fracture of the hip.

Primary arthroscopy and transarthroscopic treatment of fractures

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Since 1990, 254 cases of primary arthroscopy have been performed in injuries of the ankle joint Indications for arthroscopy are determined by the presence of haemarthrosis, for the exclusion of concomitant osteochondrial fractures, the graduation of lateral ligament ruptures on video-screening, post-traumatic locking of the joint except for osteochondritic lesions, loose bodies, hypertrophic synovitis and radiological evidence of arthrosis Arthroscopy is performed under local or general anaesthesia and using a 5-mm arthroscope with 30° telescope The findings are filmed for documentation In all, 89 per cent of patients presented a haemarthrosis with different forms of lateral ligament rupture, 32 per cent showed additional osteochondral fractures and loose bone flakes, of which 9 per cent had to be operated on transarthroscopically or by arthrotomy Lateral ligament ruptures are only treated operatively by 'held' radiograms in anaesthesia with a subluxation of the foot more than 20°. Currently, fractures of the lateral and medial malleolus are treated by transarthroscopic osteosynthesis After operation there was one case of persistent irritation of the superficial peroneal nerve It is believed that arthroscopy should be extended to the ankle joint

Prognostic indicators of multiple organ system failure and mortality in a surgical intensive care unit

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Multiple organ system failure (MOSF) is a complex syndrome with many known inter-related risk factors To account for such inter-relation, multivariate statistical methods were used to study factors related to the extent of MOSF and mortality in a large group of critically ill patients from a surgical intensive care unit (ICU). Criteria for chronic disease, malnutrition and infection were defined according to the literature A previously defined MOSF score, varying from 0 to 14, was used to quantify the extent of MOSF.

During a 1-year period (1987), 538 patients were consecutively admitted to an ICU. Mean(s.d.) age was 55 5(19 1) years Mean(s d) Acute Physiology and Chronic Health Evaluation (APACHE II) score was 5·9(5·6) Malnutrition and infection occurred in 33 per cent and 19 per cent of patients respectively Enterobacteriaceae were found in 60 per cent of infected patients. Infection was associated with an increasing MOSF score ($P < 0{\cdot}001$) Multiple linear regression selected advancing age, malnutrition, APACHE II score, shock and coma on admission, number of blood transfusions in the first 48 h, use of H_2-receptor antagonists (H_2-RA) and antacids, bacteraemia and intra-abdominal infection as independent factors related to the MOSF score Overall mortality rate was 11 per cent Mortality rate increased with rising age, malnutrition, and with the APACHE II score (all $P < 0{\cdot}001$) Furthermore, mortality was not only associated with the MOSF score, but also with the degree of malfunction within each individual organ system (both $P < 0\,001$). Multiple logistic regression selected advancing age, malnutrition, coma on admission, number of blood transfusions in the first 48 h, bacteraemia, APACHE II and MOSF score as major predictors of mortality

In conclusion, APACHE II score is positively correlated with the extent of MOSF Advancing age, malnutrition, shock and coma on admission, number of blood transfusions in the first 48 h, use of H_2-RA and antacids may impair host defences of the gastrointestinal tract and predispose to invasive infection, thereby aggravating the severity of existing MOSF These findings, together with the predominance of Enterobacteriaceae in infected patients, suggest that translocation of intestinal bacteria and endotoxin may be important in initiating and perpetuating the MOSF septic state in surgical patients with critical illness

Subtrochanteric fracture of the femur: results of treatment with the 95° condylar Blate plate, Gamma nail and dynamic condylar screw

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During a 10-year period 214 subtrochanteric fractures of the femur were treated at the Katholic University Hospital of Leuven Of these, 153 fractures were treated either with the 95° condylar Blate plate, a dynamic condylar screw (DCS), or a Gamma nail Retrospective analysis of the results was made.

A total of 77 men and 76 women were treated (mean age 64 years). Of these, 36 men and 14 women were injured in road traffic accidents. In almost all the other patients a simple fall or a fall from a height was the cause of injury The Injury Severity Score (ISS) ranged from 13 to 57 The mean ISS in men was 20, compared with 16 in women.

Of the fractures, 105 were treated with a 95° condylar Blate plate. There were six cases of delayed union (> 6 months), seven malunions and three non-unions Reoperation was necessary in four cases (three pseudarthrosis and one fracture of the Blate plate) Twenty-eight fractures were treated with a DCS Delayed union occurred in two cases, malunion in five and a reoperation was carried out twice (one cutting out and one loosening of the screws) The Gamma nail was used in 20 patients· malunion occurred in six cases and in five patients a second operation was necessary (two fractures at the tip of the Gamma nail, one Gamma nail was badly positioned and two cutting-out problems). Subtrochanteric fracture treated with a condylar Blate plate yielded better radiographically proven end results and the failure rate with this technique was less than with the DCS or Gamma nail. However, with a DCS or Gamma nail rapid mobilization is possible

Amputee sports

R.J. Watts, *Prosthetist to the British Paralympic Team 1992*

This paper covers two sporting events involving amputees, the IXth Paralympic Games held last year in Barcelona and the forthcoming sixth Whitbread round-the-world yacht race

Last year saw a spectacle that any athlete would have been proud to have participated in, the IXth Paralympic Games in Barcelona. The British Broadcasting Corporation screened a 1-h programme on the Paralympics on Christmas Eve The 1992 Paralympic Games slogan 'Sport without limits' was designed to bring two significant points into focus. the efforts made to bring about the full integration of disabled or physically challenged people through sport and the great numbers of teams and athletes participating.

The second event, the Dolphin Challenge, highlights the determination of the disabled to convert disadvantage into advantage The Dolphin project's boat was designed by Rob Humphries and built by Vision Yachts on the Isle of Wight, UK. It will be crewed completely by the disabled, blind, deaf and limb deficient. The Whitbread round-the-world yacht race will start on 25 September 1993. An estimated 30 boats will travel 32000 nautical miles in 9 months.

Outcome of patients with head injuries rescued by a helicopter emergency service in a metropolis

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This study was undertaken to demonstrate that early management of head injuries reduces disability

Head-injured patients are resuscitated at the scene by a doctor and transported to the Royal London Hospital by helicopter. Severity, type and outcome of head injury are measured using the Glasgow Coma Score, Traumatic Coma Data Bank computed tomography brain scan classification and Glasgow Outcome Scale at 6 months.

A total of 112 patients sustaining head injuries with Abbreviated Injury Score ≥ 1 were recorded between September 1990 and December 1991. At the accident scene, the mean Glasgow Coma Score was 7, pulse oximetry was reduced in 35 per cent of cases and 60 per cent of patients were ventilated Average time from injury to helicopter arrival was 24 min. Average time to remove intracranial haematomas was 189 min Some 90 per cent of patients sustaining a diffuse I head injury and 60 per cent a diffuse II injury achieved 'independence' compared with 61 per cent and 35 per cent respectively in the Traumatic Coma Data Bank ($\chi^2 = 18\ 05$, 2 d.f., $P < 0\ 001$).

Reasons for these significantly different results will be discussed in relation to the methods of measuring head injuries and achieving 'rapid resuscitation' and 'early definitive neurosurgical care'

Urology

Role of the ipsilateral testis in the contralateral biochemical changes seen after unilateral spermatic cord torsion

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Unilateral testicular torsion has been shown to cause a decrease in contralateral testicular blood flow. The stimulus triggering this contralateral change may be transmitted either neurally or humorally. An experimental study was conducted to investigate whether the presence of the ipsilateral testis is necessary for the transmission of changes in contralateral testicular perfusion seen during unilateral spermatic cord torsion. Adult male albino rats were divided into four groups, each containing ten rats. In group 1 rats, basal values of biochemical parameters were determined Group 2 rats were subjected to unilateral spermatic cord torsion in the presence of the ipsilateral testis. Rats in group 3 underwent unilateral spermatic cord torsion after ipsilateral orchidectomy. Orchidectomy was performed by transecting the gubernaculum inferiorly and the efferent ductules superiorly Testicular artery and vein were ligated at the proximal pole of the testis. The testis was excised leaving intact epididymis attached to the spermatic cord. Rats in group 4 underwent unilateral orchidectomy without torsion.

Both testes and the right kidney were harvested at the end of experiments Levels of lactic acid, hypoxanthine and thiobarbituric-reactive products of lipid peroxidation were determined in testicular tissues and kidneys. Values of these three parameters obtained from rats in the orchidectomy alone group (group 4) did not differ significantly from basal values ($P > 0\cdot05$) Lactic acid, hypoxanthine and lipid peroxide levels all increased significantly in the contralateral testis but not in the kidney after unilateral spermatic cord torsion in the presence of the ipsilateral testis (group 2 animals) compared with basal values ($P < 0\cdot05$) Unilateral spermatic cord torsion in the absence of the ipsilateral testis (group 3) also produced significant increase in the values of intratesticular biochemical parameters in the contralateral testis compared with basal values ($P < 0\cdot05$) but, again, changes in the kidney were not significant ($P > 0\cdot05$).

It is concluded that the ipsilateral testis does not play a role in transmitting these contralateral changes

Morbidity of urinary diversion in patients undergoing pelvic exenteration for gynaecological malignancy

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A total of 97 patients undergoing pelvic exenteration for gynaecological malignancies (anterior 36, posterior 26, total 25, atypical ten) from 1980 to 1992 are reported. Of these, 69 patients had undergone previous radiotherapy Sixty-three urinary diversions were performed, 15 direct cutaneous ureterostomies, four digestive conduits, one enterocystoplasty, and one wet colostomy. Altogether, 112 surgical procedures associated with pelvic exenteration were performed, including six nephrectomies, seven ureteric reimplantations and seven partial cystectomies.

There were seven (7 per cent) short-term urinary complications (three urinary fistulas and four urinary and digestive fistulas on irradiated bowel). There were 37 surgical complications in 29 patients The majority of short-term surgical complications occurred in patients with previous radiotherapy > 45 Gy ($P < 0\cdot05$), total pelvectomy ($P < 0\cdot01$) and ileal conduit used for urinary diversion ($P < 0\cdot05$). There were ten long-term urinary complications· stenosis of cutaneous ureterostomy in five, stenosis of ureteroileal anastomosis on ileal conduit in two, and urinary fistula in three

Direct cutaneous ureterostomy is the simplest procedure for urinary diversion, but necessitates two stomas and has a high rate of stomal stenosis Ileal conduit requires only one stoma but has a high rate of fistula in irradiated patients. The use of a segment of unirradiated bowel (jejunum or transverse colon) constitutes the preferred method of urinary diversion in patients undergoing pelvic exenteration after previous radiotherapy Improved perioperative support and surgical technique have decreased postoperative mortality and morbidity rates. We propose pelvic reconstruction (i e. coloanal anastomosis, vaginal reconstruction and continent urinary diversion) after pelvic exenteration in young patients with gynaecological malignancy

Prostate thermotherapy: subjective and objective outcomes correlated in 6-month follow-up study of treatment *versus* sham groups

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The technique of prostate thermotherapy has been fiercely criticized as a treatment for benign prostatic hypertrophy (BPH) bladder outflow obstruction on account of the insignificant improvement in urinary flow rate. Enthusiasts of the technique point to clinical response and a uroflow increase of 30 per cent which withstands statistical testing but compares poorly with increase after endoscopic resection Uroflow alone cannot be used to quantify outflow obstruction.

A total of 118 patients were entered into a randomized trial of active *versus* sham treatment. The effects of thermotherapy with the Thermex II system, 48°C for 3 h, were assessed by fill-void cystometry. Measurements were made before treatment and 6 months after treatment

In the treatment group ($n = 99$), 93 per cent of patients had a useful improvement. Of the sham group ($n = 19$), 6 per cent had a useful improvement ($P < 0\cdot005$) After analysis of the first 79 patients in the good response group there was a fall in voiding pressure of 35 per cent (range 28–55 per cent) ($P < 0\cdot001$), and a 34 per cent increase in uroflow ($P = 0\cdot01$) indicating a definite reduction in outflow resistance. In the poor symptomatic responders and shams, there were no consistent changes in the measured parameters

In conclusion, this treatment not only affords symptomatic relief but also reduces outflow resistance in patients with BPH-associated outflow obstruction.

Magnetic resonance imaging of urinary calculi

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Accurate prediction of the response of a calculus to lithotripsy is still not possible. Certain stones, particularly calcium oxalate monohydrate (brushite), cystine and uric acid, are known to be hard and consequently have a poor response to extracorporeal shockwave lithotripsy (ESWL) This study reports the use of magnetic resonance imaging (MRI) *in vitro* to distinguish between stones of varying chemical types

Sixty calculi were placed in a phantom in the head coil of a Siemens Magnetom 1·5-T MRI scanner. T1-weighted (TR 600 ms, TE 15 ms), T2-weighted (TR 2500 ms, TE 90 ms), and proton density (TR 2500 ms, TE 20 ms) images were taken. The chemical composition of the stones was determined by infra-red spectroscopy

Significant differences were noticed between calcium oxalate and uric acid stones ($P < 0\cdot002$) and uric acid and struvite stones ($P < 0\cdot04$) on T2-weighted images, and between uric acid and struvite stones on proton density images ($P < 0\cdot04$) Several other comparisons failed to reach statistical significance because of the small group sizes Further work is continuing on larger samples correlating the findings with results of ESWL, to determine whether MRI might be used as an *in vivo* predictive test for the success of lithotripsy.

Low-angle X-ray diffraction of urinary calculi

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X-ray diffraction is a well established and reproducible technique for analysing urinary calculi, capable of differentiating compounds present within mixtures of 2 mg or less The first use of low-angle X-ray diffraction (LAXD) for the analysis of intact urinary calculi is reported.

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Sixty calculi were analysed using a 70 kV_P X-ray beam. Data were collected using a lead-shielded germanium photon detector and analysed using a multichannel analyser linked to a microcomputer. The chemical composition of the stones was determined by infra-red spectroscopy

	kV$_P$ of signal peaks			
Calcium oxalate		33	41	49
Uric acid	25	38		50
Struvite		39		
Apatite			42	
Ammonium urate		38		
Saline solution (standard)		38		

These preliminary results show that LAXD is capable of differentiating between the common types of calculi. Further work is being performed to characterize larger numbers of calculi The low energy of the beam used means that this technique may prove suitable for *in vivo* work, and further studies are in progress to correlate the results of LAXD with stone fragility after lithotripsy

Evaluation of effect of time on recollection of patient-perceived outcome in prostatectomy

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In excess of 4500 patients were recruited from 105 contributing surgeons into a multiregional audit of structure, process and patient-perceived outcome in men undergoing operative prostatic procedures over a 6-month period. The study is under the auspices of the British Association of Urological Surgeons and the Association of Surgeons of Great Britain and Ireland.

Patients were asked to recollect symptoms before and after an operative procedure on the prostate gland A validation study of recollected symptoms was undertaken in 100 consecutive men undergoing prostatic surgery in Chesterfield and North Derbyshire Hospitals Each patient was asked to complete a symptom profile of the American Urological Association (AUA-7), and both disease-specific and general quality-of-life score, Ware's Short Form (SF-36) in the preoperative phase and at a 3-month postoperative interval.

Analysis of stability of scores over time, together with an estimate of correlation between actual and recollected scores, has yet to be undertaken. It is hoped that the effects on symptom recollection of either a strongly positive or an adverse outcome will be evaluated by comparison with global measures of satisfaction.

The implications of a retrospective method of data collection for the estimation of post-discharge surgical outcome are significant Proven validity of this method of data collection enables post-discharge outcome to be determined using a preoperative baseline without identifying patients before the procedure. Resultant benefits are likely to include an analysis of only one data set, increased data capture, reduction in matching error, decrease in patient's time commitment, together with considerable cost savings The results of this study will have implications on the design of all future studies of post-discharge surgical outcome

p53 expression in urothelial cell cultures and tissues from healthy people and patients with bladder cancer

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Expression of a stable form of p53 has been associated with many tumours and is thought to indicate loss of the tumour suppressor function associated with the wild-type protein The expression of p53 in paraffin-embedded bladder cancers and normal urothelial cell cultures derived from healthy individuals and patients with bladder cancer has been examined.

Using the p53-240 and p53-DO7 antibodies, 20 of 22 paraffin-embedded bladder cancer specimens were found to express p53 All normal urothelial specimens from both healthy and cancer-bearing patients were negative for p53 expression In urothelial cell cultures derived from healthy individuals >10 per cent of cells were observed to be positive in nine of 37 cases. In cultured normal urothelium derived from patients with bladder cancer, staining was positive in 11 of 11 cases

It is concluded that stable p53 protein is present in most bladder cancers and also in histologically normal areas of urothelium distant from the site of the disease Expression of this protein was not observed in paraffin-embedded material but was apparent on culturing the cells. The presence of a subgroup of normal patients whose urothelium expressed stable p53 on culturing requires further study

New tumour node metastasis classification for prostate cancer: pathological features of cancers detected by prostate-specific antigen alone

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In 1992 the tumour node metastasis (TNM) classification system for prostate cancer (Union Internacional Contra la Cancrum and American Joint Committee on Cancer) was revised in several important ways. The new system includes a category (T_{1c}) for patients with non-palpable cancer detected by systematic biopsy as a result of an elevated serum prostate-specific antigen (PSA) level. It includes in the T_2 category cancers visible by transrectal ultrasonography in addition to those palpable by digital rectal examination To assess the clinical and pathological features of cancers in each of these categories, an analysis was carried out of 318 patients with prostate cancer assessed as clinical stages T_{1-3} N_0 or N_X M_0 and treated by radical retropubic prostatectomy.

In general, tumour volume increased with increasing clinical stage ($P < 0.0001$) while the percentage with a tumour confined to the prostate decreased ($P < 0.0001$). Of particular interest were 15 patients with T_{1c} tumours. None of these cancers was palpable or visible by ultrasonography Although the tumours were relatively small (median volume 0·72 cm^3), seven (47 per cent) were > 1 cm^3, eight contained a primary or secondary component of poorly differentiated cancer and four extended outside the prostate Of 232 patients with a T_2 cancer, 16 had a non-palpable tumour that was visible using ultrasonography and 21 a palpable tumour not ultrasonographically visible. These tumours were similar in size and pathological features.

The new TNM staging system provides appropriate categories for the inclusion of non-palpable prostate cancers detected using new diagnostic tests and appears to reflect the extent of the cancer and the prognosis of the patient.

Inflatable penile prostheses in the management of erectile impotence

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Inflatable prostheses restore voluntary erection while remaining cosmetically acceptable. Twenty patients with erectile impotence, aged 22–65 years, underwent implantation of an AMS inflatable penile prosthesis Nineteen had an organic aetiology, with diabetes mellitus the most common primary disorder Sixteen patients received the AMS 700 CX prosthesis and two the AMS 700 Ultrex. Devices were implanted through a transverse infrapubic incision Hydroflex prostheses were inserted in the other two patients through a penoscrotal approach Before operation all patients underwent rigorous local skin preparation with antiseptic solutions. Broad-spectrum antibiotics were used All patients were reviewed after operation and instructed in the use of the device Follow-up ranged from 7 to 93 months There were no mechanical complications Surgical complications including infection of the prosthesis, scrotal haematoma and cylinder erosion, were each seen in one patient Nineteen patients maintained long-term satisfaction with the prosthesis Insertion of an inflatable penile prosthesis restored satisfactory erectile function in 95 per cent of patients

Rome pouch: a preperitoneal continent ileal reservoir with hydraulic valve

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A continent ileal reservoir using the terminal ileum in a preperitoneal position has been used in 18 urological patients after cystectomy. The ureters were implanted using the Le Duc–Camey technique; the Benchekroun valve was used as a continent mechanism

The mean(s.d.) postoperative neobladder capacity was 350(60) ml, which increased to 600(90) ml after 1 year. There was no ureteric reflux or fistula formation during a follow-up ranging from 12 months to 4 years No complications with the stoma occurred.

This technique of continent diversion is particularly recommended for patients undergoing cystectomy.

Vascular

Leg compression and microcirculation

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The reasons for the efficacy of compression treatment in venous disease are not clear. Laser Doppler fluxmetry has been used to assess the effects of external compression on skin microcirculation. Fifteen patients with lipodermatosclerosis (LDS) because of chronic venous insufficiency as proven by colour duplex scanning and 15 control subjects were studied in the supine position. The laser probe, installed in a polythene chamber, was applied to the lower leg underneath a blood pressure cuff. Pressures were applied in increments from 10 to 100 mmHg. Laser Doppler flux (LDF), blood cell velocity (BCV) and concentration of moving blood cells were recorded.

	Pressure (mmHg)		Percentage increase	Median difference (95% confidence interval)
	0	20		
LDF (arbitrary units)				
Control	33 (22–41)	41 (29–54)	17	10 (4–18)
LDS	50 (38–60)	65 (46–118)	33	13 (3–24)
BCV (arbitrary units)				
Control	21 (11–26)	28 (16–46)	40	11 (4–22)
LDS	9 (4–17)	21 (6–30)	79	7 (3–21)

Values are median (interquartile range)

Compression of the skin at 20 mmHg resulted in an increase in LDF and BCV in normal and liposclerotic skin. Higher levels of compression resulted in a progressive fall in LDF and BCV. This study suggests that compression treatment may achieve part of its effect by causing an increase in the microcirculatory flow velocity.

Acetylcholine sweat-spot test: an easy and effective method for selecting patients for lumbar sympathectomy

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Lumbar sympathectomy is a useful low-risk procedure for treating patients with ischaemic limbs, but its efficacy is not easily predicted. A possible explanation for this may be pre-existing damage to the sympathetic fibres because of long-lasting diabetes or from the ischaemic disease itself. The acetylcholine sweat-spot test (SST) is an easy and inexpensive test for evaluating sympathetic integrity.

Sixteen patients selected for either surgical or chemical lumbar sympathectomy entered this preliminary study. The SST was performed before operation and 1 month after operation on the foot of the ischaemic leg. The results were evaluated clinically by a preoperative and postoperative questionnaire; in five patients, preoperative and postoperative photoplethysmography, capillaroscopy, laser Doppler, oximetry and Windsour index was used. Four patients had a normal SST, five had moderate denervation and seven had severe or complete denervation. At 1 month after the operation the SST indicated a complete denervation in all patients except two; one of these had undergone chemical sympathectomy. Apart from the latter two patients, whose sympathetic activity persisted and in whom the operation failed, clinical results in the first two groups were fairly good, whereas no result was obtained in those with pre-existing damage to the sympathetic system.

A good correlation was found between clinical data and those from the objective measurements with photoplethysmography, capillaroscopy, laser Doppler, oximetry and Windsour index. These preliminary results indicate that the SST may be a helpful method for selecting patients for lumbar sympathectomy.

Hyperamylasaemia in ruptured aortoiliac aneurysm: prevalence and prognostic implications

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Serum amylase activity was measured at presentation in 25 consecutive patients with ruptured aortoiliac aneurysm. Twenty-three patients survived to have serum amylase activity measured. The aims of the study were to determine the prevalence of hyperamylasaemia (serum amylase level > 340 units l^{-1}) and its prognostic significance. The 30-day mortality rate and development of specific major postoperative complications were documented. Serum amylase was correlated with urea and creatinine concentration and length of stay in the intensive care unit (ITU).

Hyperamylasaemia occurred in ten (40 per cent) of the 25 patients and was present on admission in four of these. There were two perioperative deaths from haemorrhagic shock. Of the remaining 23 patients, 14 (group 1) made an uncomplicated recovery and nine (group 2), six of whom died, developed one or more complications. At all three times of sampling, serum amylase activity was significantly higher in group 2.

	Admission	Day 1	Day 2
Group 1 (n = 14)	212(12)	213(27)	182(28)
Group 2 (n = 9)	348(53)	631(145)	455(116)
P*	<0.025	<0.001	0.01

Values are mean(s.e.m.) serum amylase level expressed in units l^{-1} (laboratory normal is < 340 units l^{-1}). *Mann–Whitney U test

Hyperamylasaemia was significantly more prevalent in patients who developed complications (P = 0.0007, Fisher's exact test). In addition there was a significant positive correlation, independent of renal function, between serum amylase at presentation and ITU stay (r = 0.78). Hyperamylasaemia is common within 48 h of presentation with ruptured aortoiliac aneurysm. It is associated with a complicated postoperative course.

Intra-arterial thrombolysis for lower-limb ischaemia in a district general hospital

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Intra-arterial thrombolytic therapy is the treatment of choice for acute lower-limb ischaemia when the duration of therapy will not compromise limb viability.

A prospective study carried out at a district general hospital with basic radiology facilities is described. A total of 24 consecutive patients (median (interquartile range (i.q.r.)) age 75 (66–88) years) presenting with acute lower-limb ischaemia secondary to thrombotic arterial occlusion underwent urgent intra-arterial thrombolytic therapy using streptokinase (n = 23) or tissue plasminogen activator (n = 1). Thrombolysis was monitored daily by angiography. The median (i.q.r.) duration of intra-arterial thrombolytic therapy was 3 (2–4) days. Intra-arterial thrombolytic therapy alone was performed in 13 patients and an adjuvant angioplasty or thrombectomy in 11.

An improvement in ischaemic symptoms was observed in ten of 13 patients who received intra-arterial thrombolytic therapy alone, in six of seven who also underwent angioplasty and in three of four who also required thrombectomy. After treatment, the median (i.q.r.) ankle:brachial pressure index was increased to 0.5 (0–0.8) (n = 23) compared with 0 (0–0.4) (n=24) at presentation (P = 0.017, paired Wilcoxon test). The 30-day limb salvage and mortality rates were 65 and 17 per cent respectively.

Intra-arterial thrombolytic therapy, modified for use in a district general hospital, was effective in saving acutely ischaemic limbs used either on its own or to facilitate more established limb salvage procedures.

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Rare causes for occlusion of the popliteal artery

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If claudication appears in young athletic people without signs of generalized arteriosclerosis or evidence of other risk factors, then the popliteal artery compression syndrome should always be taken into consideration in the differential diagnosis. This is of great importance in view of early surgical treatment, because a delay in the operative procedure could result in complications such as an acute occlusion or distal embolization. Using five patients (one with an entrapment syndrome, one with a soleus syndrome, one with cystic adventitial degeneration of the popliteal artery and two with exostoses of the femur and the tibia), the clinical, diagnostic and surgical peculiarities of these rare conditions are reported. The diagnosis was confirmed by arteriography in all cases. The therapy and results are summarized, 1·5–4 years after operation all patients are symptom-free.

Patient no	Age (years)	Sex	Diagnosis	Surgery	Follow-up (years)
1	48	M	Entrapment syndrome	Resection, prosthesis interposition (PTFE)	3
2	25	F	Soleus syndrome	Tendon splitting	1·5
3	25	M	Cystic adventitial degeneration	Vein graft interposition	4
4	39	F	Exostosis (femur)	Exostosis excision, vein graft interposition	4
5	22	M	Exostoses (femur, tibia)	Exostosis excision, desobliteration, vein patch	3

PTFE, polytetrafluoroethylene

Thromboprophylaxis in elective abdominal surgery with a low molecular weight heparin (dalteparin): a multicentre double-blind trial in 2069 patients of two different doses started the evening before surgery

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Low molecular weight heparin (LMWH) is effective for thromboprophylaxis and a convenient method is to start treatment the evening before surgery. The optimal dose in high-risk general surgery is not yet established.

The aim of this study was to compare doses of 2500 *versus* 5000 anti-Xa units of LMWH (dalteparin) in elective general abdominal surgery, starting the evening before surgery and then every evening for 1 week.

A prospective, randomized, double-blind multicentre trial was performed. Deep vein thrombosis (DVT) was detected with a fibrinogen uptake test. Bleeding complications were recorded and classified. Analysis was performed on an intention to treat basis.

A total of 2097 patients were randomized and 28 were excluded after randomization. Some 66 per cent were operated on for malignant disorders, DVT occurred in 12·6 per cent in the 2500 unit group and in 7·7 per cent in the 5000 unit group ($P < 0.001$). The 30-day mortality rate was 3·2 per cent, without difference between the groups. There was one fatal pulmonary embolism. Bleeding complications occurred in 2·7 per cent in the 2500 unit group and in 4·7 per cent in the 5000 unit group ($P = 0.02$). Bleeding was of minor clinical importance.

Dalteparin, in the dose of 5000 anti-Xa units commenced the evening before surgery, has a good thromboprophylactic effect in high-risk general surgery at a cost of small bleeding risk. A dose of 2500 units is too low. The overall frequency of fatal pulmonary embolism is extremely low.

Vascular access and its complications in patients with chronic renal failure undergoing haemodialysis

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A total of 226 arteriovenous (AV) anastomosis operations and 49 arteriovenous polytetrafluoroethylene (PTFE) graft operations were performed on 221 patients with chronic renal failure admitted to the haemodialysis centre of Goztepe Social Insurance Hospital and the General Surgery Department of Kartal Hospital, in Istanbul. Ages of the patients ranged from 13 to 85 years, with 84 (38 per cent) female and 137 (62 per cent) male. A large number of patients were between 50 and 60 years of age.

Of the 226 AV anastomosis operations performed, 114 (50·4 per cent) were snuff-box (longitudinal), 52 (23·0 per cent) were on the wrist area and 60 (26·5 per cent) were in the antecubital fossa (brachiocephalic). Of the 49 PTFE graft operations, five (10 per cent) were between the femoral artery and the saphenous vein (loop) and 44 (90 per cent) were between the brachial artery and the axillary vein (straight).

In patients with AV anastomosis, 22 thrombectomy procedures, three repairs of a pseudoaneurysm and 12 fistula ligation procedures were performed for the management of complications. In patients with PTFE grafts, eight thrombectomy and five graft excision procedures had to be performed. At 1 year, the mean patency rate of AV anastomosis was 77 per cent and 63 per cent for PTFE graft operations.

In all patients, the flow rate in both early and late postoperative periods was measured by B-mode Doppler imaging. The mean flow rate was determined as 90 cm s^{-1}

Internal vessel occluders facilitate distal anastomosis

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When performing an anastomosis at the infrageniculate level, blood flow is traditionally arrested using vascular clamps or tourniquet control after limb exsanguination. While placing 185 *in situ* saphenous vein bypasses to the tibial level for limb salvage, the 'Flo-Restor' internal vessel occluder was used to facilitate construction of each distal anastomosis. These silicone devices are manufactured in a range of sizes to accommodate different vessel calibres.

After surgery, all patients were monitored prospectively with colour flow duplex scanning. The authors were particularly interested in velocity changes at the distal anastomosis. Of ten revision operations performed in the first month, two were related to the distal anastomosis but involved only the graft hood. At late follow-up, seven bypasses had significant duplex velocity changes at the distal anastomosis. Arteriography showed apparent disease progression in the artery in one case only. In another patient, a distal anastomotic pseudoaneurysm was detected and corrected at 3 months. The cumulative 60-month primary and secondary patency rates in this series were 70 and 84 per cent respectively.

It is concluded that the Flo-Restor is a useful device. It reduces dissection, avoids clamp trauma to calcified vessels and controls blood flow satisfactorily. The data show that with the Flo-Restor distal anastomoses can be constructed safely and the incidence of arterial anastomotic narrowing is negligible.

Neuropathy in chronic venous insufficiency

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There have been few studies on the peripheral nervous system in patients with chronic venous insufficiency. The aim of the present study was to determine whether patients with chronic venous insufficiency and lipodermatosclerosis have a higher prevalence of neuropathy than normal subjects.

Forty patients with lipodermatosclerosis and 35 age-matched normal controls were examined for neuropathy using three methods of testing. The threshold to warming was used to assess small unmyelinated C fibres. The threshold to cooling and vibration was used to assess larger myelinated fibres. The threshold to warming and cooling was measured on the sole of the foot using a purpose-built instrument controlled by computer with specially written software. The threshold to vibration was measured on the big toe using an Ohio biothesiometer. Results were analysed using the Mann–Whitney *U* test.

	Threshold to heating (°C)	Threshold to cooling (°C)	Threshold to vibration (arbitrary units)
Controls*	1·2 (0·2–3·5)	0·2 (0·1–0·3)	12·0 (8·5–27·5)
Lipodermatosclerosis*	5·3 (0·1–9·1)	0·2 (0·1–0·4)	22·0 (13·0–31·0)
P	0·005	0·9	0·03
95% c.i. of difference	−0·3 to −3·8	0·1 to −0·1	0·0 to −12·0

* Values are median (interquartile range). c.i., Confidence interval

These results show that there is a peripheral neuropathy in patients with lipodermatosclerosis, as indicated by an increase in the thresholds to warming and vibration. Neuropathy in patients with lipodermatosclerosis may explain the vulnerability of such patients to skin ulceration.

Granulocyte elastase release in chronic venous disease of the lower limb

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It has been suggested that neutrophil trapping and activation may result in the pathogenesis of skin changes seen in longstanding venous disease. This study measured plasma elastase as a marker of neutrophil activation in blood taken from an arm vein in three groups of 15 patients with uncomplicated varicose veins, varicose veins associated with lipodermatosclerosis (LDS) and venous ulceration. Results were compared with values obtained from three groups of age- and sex-matched normal controls. Blood was also taken for full blood count, including neutrophil count.

	Control	Varicose veins	Control	LDS	Control	Venous ulcers
Elastase (ng ml^{-1})*	18·05 (12·6–30)	25·6 (20·4–39·8)	17·7 (12·6–21·2)	22·1 (19–33·9)	18·8 (12·4–34·3)	26·0 (22·3–39·5)
Difference between medians	8·0		7·0		8·5	
95 per cent confidence interval for difference	0·8–14·0		1·4–13·5		1·4–14·1	
P†	0·0344		0·007		0·0265	

*Values are median (interquartile range). †Mann–Whitney *U* test

There was a significantly raised circulating plasma elastase level in all three patient groups, with no correlation between elastase and neutrophil levels, suggesting that neutrophil activation had occurred. There was a correlation between plasma elastase and age in the control group ($P = 0{\cdot}045$), but not with sex or neutrophil count. This *in vivo* study suggests neutrophil activation in venous disease.

Thromboxane antagonism prevents hindlimb ischaemia–reperfusion-induced gut damage

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Abnormal intestinal permeability has been linked with postoperative multiple organ failure. Previous studies have demonstrated that hindlimb ischaemia and reperfusion leads to abnormal permeability. The aim of this study was to determine whether thromboxane receptor antagonism with ICI 192605 could prevent this abnormal permeability.

Anaesthetized male rats were randomized to three groups: group 1 had 3 h hindlimb ischaemia and 2 h reperfusion ($n = 6$), group 2 were as group 1 with an intravenous infusion of the solvent dimethyl sulphoxide (DMSO) ($n = 6$), and group 3 were as group 1 with an infusion of ICI 192605 in the solvent DMSO ($n = 6$). Intestinal permeability was assessed by electron microscopic penetration of the permeability marker horseradish peroxidase beyond the intracellular junction of terminal ileal enterocytes.

All six rats in group 1 demonstrated abnormal permeability after reperfusion, four of the six animals in group 2 demonstrated abnormal permeability after the infusion of DMSO alone (*P* not significant *versus* group 1); however, no animal in group 3 demonstrated abnormal permeability after the infusion of ICI 192605 ($P < 0{\cdot}05$ *versus* group 1, Fisher's exact test).

Thromboxane receptor antagonism prevents the abnormal permeability that follows hindlimb ischaemia and reperfusion. This study suggests a possible role for such agents in the field of vascular surgery where reperfusion injury occurs after aortic cross-clamp release.

Neutrophil and endothelial mediators in postischaemic alterations to skeletal muscle blood flow

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Endothelial and neutrophil-derived thromboxane A_2, leukotriene B_4 and elastase are putative mediators of reperfusion injury but their relative roles are unknown. After 6 h of unilateral hindlimb ischaemia blood flow was measured in the gastrocnemius muscle of ten rats after 10, 120 and 240 min of reperfusion (perfusion index), and levels of thromboxane A_2, leukotriene B_4 and elastase were measured in the venous blood of reperfused limbs. The results (median (interquartile range)) were compared with values obtained in ten normal controls. Perfusion indices in normal rats at 10, 120 and 240 min were 1·05 (0·68–1·18), 0·97 (0·79–1·13) and 1·01 (0·73–1·16) respectively, and in rats that had undergone ischaemia–reperfusion 0·08 (0·01–0·13), 0·29 (0·09–0·59) and 0·05 (0·01–0·14) respectively. Thus the latter group demonstrated low reflow (10 min, $P < 0{\cdot}01$ *versus* controls), relative reperfusion (120 min, $P < 0{\cdot}05$ *versus* controls) and reperfusion injury (240 min, $P < 0{\cdot}01$ *versus* controls). Levels of thromboxane A_2, leukotriene B_4 and elastase in normal rats were 288 (187–300), 124 (75–172) and 13 (0–17) respectively. In reperfused rats elastase levels, reflecting neutrophil recruitment/activation, peaked at 240 min (25 (16–31), $P < 0{\cdot}01$ *versus* controls). Values measured at 10 and 120 min were 15 (0–34) and 0 (0–23) respectively, and were not significantly different from controls. Leukotriene B_4 levels, indicative of neutrophil chemotaxis, peaked earlier at 120 min (190 (138–203), $P < 0{\cdot}05$ *versus* controls). Concentrations at 10 and 240 min were 126 (103–183) (*P* not significant) and 195 (159–211) ($P < 0{\cdot}05$) respectively. In contrast, thromboxane A_2 levels were highest at 10 min (1758 (940–2175), $P < 0{\cdot}001$ *versus* controls) and then fell to 1150 (580–1550) and 733 (340–880) at 120 and 240 min respectively. These results suggest that neutrophil recruitment and activation is a late event, and that the vasoconstrictor thromboxane A_2 rather than the neutrophil initiates low reflow.

Effect of depletion of circulating neutrophils on reperfusion injury

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Neutrophils have been implicated in the pathogenesis of reperfusion injury. The effect of neutrophil depletion on gastrocnemius muscle viability, oedema and myeloperoxidase activity was assessed in a rat model. Rats were subjected to unilateral hindlimb ischaemia for 6 h and reperfusion for 4 h. Ten normal (no ischaemia), ten control (6 h ischaemia plus 4 h reperfusion) and ten neutropenic (given antineutrophil serum) rats were studied. Indices of gastrocnemius muscle viability and oedema were calculated (study limb:contralateral normal limb). Antineutrophil serum reduced median (interquartile range) neutrophil counts from 825 (560–1355) mm^{-3} in controls to 55 (40–145) mm^{-3} ($P < 0{\cdot}001$, Mann–Whitney *U* test).

	Viability index	Oedema index	Myeloperoxidase activity
Normal	1·00 (1·00–1·00)	1·00 (0·98–1·01)	0·05 (0·00–0·10)
Control	0·53 (0·33–0·61)	1·61 (1·28–1·69)	2·95 (1·70–4·70)
Neutropenic	1·00 (1·00–1·00)	1·64 (1·37–1·73)	0·30 (0·10–0·50)

Values are median (interquartile range)

Ischaemia–reperfusion caused muscle infarction, oedema and neutrophil recruitment (control *versus* normal rats $P < 0{\cdot}001$, all parameters). In rats treated with antineutrophil serum muscle necrosis was prevented and neutrophil recruitment was markedly attenuated ($P < 0{\cdot}001$ *versus* controls). However, muscle oedema still occurred (P not significant *versus* controls). These results confirm a role for neutrophils in the pathogenesis of postischaemic muscle necrosis but suggest that disruption of the endothelial barrier occurs independently.

Vein graft adaptation

A.H. Davies, T.R. Magee, J.K. Hayward, R.N. Baird and M. Horrocks, *Vascular Studies, Bristol Royal Infirmary, Bristol, UK*

The diameter of the long saphenous vein has been shown to affect the outcome of femorodistal bypass Many surgeons regard a vein with a diameter of <3 mm as unsuitable. It is well documented that vein grafts dilate

The long saphenous vein was studied in 70 patients undergoing femorodistal bypass. Diameter measurements were performed using a duplex scanner at the groin, mid-thigh and knee At the latter two points, diameter measurements were performed with proximal venous occlusion at 1-min time intervals Diameter measurements were repeated 7 days and 6 months after surgery

The preoperative mean groin diameter was 4·9 (95 per cent confidence interval 3·1–6·8) mm. Diameter measurements at the other points are shown.

	Non-dilated (mm)	Dilated (mm)	7 days (mm)	6 months (mm)
Mid-thigh	4·2 (2·5–5·9)	5·1 (3·1–7·1)	5·4 (3·7–6·7)	5·4 (3·7–7·1)*
Knee	3·8 (2·2–5·6)	4·8 (3·4–6·2)	4·8 (4·1–6·5)	5·0 (3·0–7·0)*

Values in parentheses are 95 per cent confidence intervals. *$P < 0{\cdot}01$ (analysis of variance)

Dilatation occurred in eight of ten veins with a diameter < 3 mm, so that all became > 3 mm These results suggest that, by using a technique of venous occlusion at the time of preoperative vein mapping, the functional diameter of the vein can be predicted and vein utilization increased

Augmented Doppler evaluation of the distal run-off

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The quality of the distal run-off is one of the most important factors in determining the outcome following femorodistal reconstruction.

Ninety patients undergoing femorodistal bypass had preoperative intra-arterial digital subtraction angiography (DSA) and Doppler evaluation with pulse-generated augmentation (PGR) The results were compared with postoperative DSA.

Underestimation of the distal run-off calf vessels by preoperative DSA occurred in 34 per cent of patients

	Preoperative DSA	PGR	Postoperative DSA
Artery identified at the calf ($n = 90$)			
Posterior tibial	61	73	71
Anterior tibial	39	62	62
Peroneal	33	63	57
Quality of arch			
Complete	11	15	14
Incomplete	59	67	68
Occluded	20	8	8

Grafts performed in a limb with a below-knee PGR score $\leqslant 3$ had a 12-month cumulative patency rate of 73 per cent compared with 85 per cent in those with a below-knee PGR score $\geqslant 4$ ($P = 0{\cdot}08$, log rank test, $P = 0{\cdot}06$, Wilcoxon test). The 12-month cumulative patency rate for grafts with complete, incomplete or occluded arches, as defined by PGR, was 78, 90 and 38 per cent respectively ($P < 0{\cdot}0001$, log rank and Wilcoxon tests)

Preoperative evaluation of the distal run-off before femorodistal bypass should not be based on DSA alone and can be predicted by PGR

Popliteal artery entrapment syndrome

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Popliteal artery entrapment is described with increasing frequency in the world literature. It is due to an anomalous inter-relationship of the popliteal artery and its surrounding structures. A total of 34 cases in 25 patients (21 men) of mean(s d.) age 34·2(14·7) years were treated surgically Symptoms reported before operation were classified into three groups mild (17 limbs), claudication > 100 m (nine limbs), other – severe claudication, rest pain and necrosis (eight limbs) Preoperative arteriography showed arterial occlusion in eight limbs, stenosis in eight and aneurysm in two In 14 limbs stenosis or occlusion was shown after manipulation In two limbs diagnosis was performed on the basis of venography showing popliteal vein entrapment. Ten different anatomical variants were seen In 76 per cent of cases the medial gastrocnemius muscle was involved. Surgical treatment consisted of division of the anomalous structure in 21 cases In 12 cases a vascular reconstruction was required, while one case was explored and not reconstructed. Optimal results were obtained in patients treated by musculotendinous sectioning (patency rate 95 per cent, mean follow-up 57 months) When grafting was required the primary patency rate was 58 per cent (mean follow-up 61 months) It is concluded that popliteal artery entrapment should be diagnosed and treated as soon as possible, to limit surgical treatment and avoid the need for vascular reconstruction.

Arterial insufficiency and large leg ulcers

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Arterial gangrene generally begins on pressure areas on the side of the foot or heel. However, in a small proportion of patients it commences over the leg and may be mistaken for venous ulceration.

Experience in the vascular investigation and treatment of a consecutive series of 42 patients who had large (surface area $> 100\,\text{cm}^2$) leg ulcers is reviewed. The 42 patients were studied prospectively, all had non-invasive vascular investigations. Seventeen patients had significant arterial disease and underwent arteriography Twelve patients had a superficial femoral artery occlusion, four popliteal aneurysm thrombosis and one an arteriovenous fistula Fourteen patients underwent arterial bypass graft. All patients had skin grafting Those with venous disease had compression bandaging

The 15 arterial ulcers healed in 28 days after a successful graft This was significantly more rapid than in the 25 venous ulcers (mean 37 days). In addition, 75 per cent were still healed after 2 years compared with 57 per cent of venous ulcers. Arterial insufficiency occurs in over 30 per cent of patients with large leg ulcers. If treated successfully, prompt healing of the ulcer can be expected

Videothoracoscopic sympathectomy for secondary Raynaud's syndrome

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Secondary Raynaud's syndrome is an indication for thoracic sympathectomy. Warm flushed hand and improvement of hyperhidrosis are useful effects and there is significant improvement of peripheral hand circulation on the operated side. Conventional operation via minithoracotomy is too invasive for resection of a 3-cm segment of the sympathetic trunk. Rib fractures and spreading of the intercostal space are disadvantages of minithoracotomy, which have left sympathectomy with a bad reputation in the past. Using thoracoscopy with laparoscopic instruments and working in a controlled pneumothorax, resection of only the rami of the stellate ganglion and not the ganglion itself is possible with an excellent endoscopic view. Three subaxillary ports give a good cosmetic result. The suction drain is removed after 24 h.

Twelve patients have been operated on in this way. One developed Horner's syndrome, showing the importance of resecting only the rami of the stellate ganglion. Wound pain had gone after 36 h. There were no deaths and only minor morbidity with superficial wound infection in one patient. The circulatory result is excellent up to 14 months, longer term results are awaited. Minimally invasive sympathectomy extends its indications without disadvantages to the patient.

Multicentre randomized double-blind trial of low molecular weight heparin and standard heparin for prevention of postoperative venous thromboembolism in major abdominal surgery

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The efficacy and safety of low molecular weight heparin (LMWH) and standard heparin in preventing postoperative venous thromboembolism were compared in a prospective double-blind randomized trial involving 3809 patients undergoing major abdominal surgery. The heparins were given before surgery and continued for at least 5 days after operation. A total of 1894 patients received LMWH and 1915 standard heparin. No difference was found in the efficacy of the two heparins. Perioperative deaths occurred in 110 patients (2·9 per cent): 63 patients (3·3 per cent) treated with LMWH and 47 (2·5 per cent) standard heparin (relative risk 1·36 (95 per cent confidence interval (c.i.) 0·93–1·97). Pulmonary emboli were detected in 27 patients (0·7 per cent), 13 (0·7 per cent) of whom were treated with LMWH and 14 (0·7 per cent) standard heparin. Sudden death occurred in eight of these and at autopsy five (0·3 per cent) and three (0·2 per cent) patients treated with LMWH and standard heparin respectively were found to have died from acute massive pulmonary embolism. Deep vein thrombosis was diagnosed in 11 patients (0·6 per cent) in each group. The safety of the heparins was assessed using objective criteria. A total of 93 incidents of major bleeding occurred in 69 patients (3·6 per cent) given LMWH compared with 141 incidents in 91 patients (4·8 per cent) treated with standard heparin. Severe bleeding occurred less frequently in patients receiving LMWH, there being 18 (1·0 per cent) affected compared with 36 (1·9 per cent) given standard heparin (relative risk 0·51 (95 per cent c.i. 0·29–0·89), P = 0·02). Similarly, wound haematomas were less common in patients receiving LMWH (27 (1·4 per cent) *versus* 52 (2·7 per cent), relative risk 0·52 (95 per cent c.i. 0·33–0·83), P = 0·007). Twenty bleeding episodes in 18 patients (1·0 per cent) treated with LMWH and 38 episodes in 33 (1·7 per cent) receiving standard heparin required further surgery, either for evacuation of a haematoma or to control bleeding (relative risk 0·55 (95 per cent c.i. 0·31–1·98), P = 0·05).

Both heparins appear to be of equal efficacy but LMWH is safer, it causes less severe bleeding, fewer wound haematomas and a smaller number of patients require reoperation to control bleeding.

Prospective randomized trial of low molecular weight heparin *versus* Persantin in femoropopliteal bypass grafts

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Late graft failure, which occurs in 30–35 per cent of patients undergoing reconstructive surgery for critical lower-limb ischaemia, presents a major clinical problem. In the majority of cases, such failure is due to intimal hyperplasia, often at the anastomotic site. Low molecular weight heparin (LMWH) may have a beneficial effect in controlling such lesions because of its proven antithrombotic and antiproliferative properties. A prospective randomized trial was therefore designed to compare the efficacy of LMWH *versus* conventionally used therapy of aspirin and dipyridamole in the maintenance of graft patency.

A total of 206 patients over 40 years of age with radiographically proven occlusive arterial disease and suffering from critical lower-limb ischaemia were randomized to receive either LMWH, 2500 units daily subcutaneously, or aspirin 300 mg and Persantin (dipyridamole) 100 mg daily. Each patient was assessed 1, 3, 6 and 12 months after inclusion in the trial.

A standard technique was used for performing femoropopliteal bypass. All risk factors likely to be related to graft failure or bleeding were recorded throughout the observation. Follow-up observations included clinical assessment, ankle:brachial pressure index, duplex ultrasonography and magnetic resonance imaging, particularly for assessment of the anastomotic site.

In all, 200 patients have been followed, nine died, seven in the LMWH group and two in the Persantin group (P = 0·12). The results of graft patency analysed over 1, 3, 6 and 12 months were as follows. There was a marked trend in graft survival in the LMWH group throughout the trial. This difference reached statistical significance with a 20 per cent increase in the graft patency rate observed at 6 months (relative risk 1·20 (95 per cent confidence interval (c.i.) 1·03–1·10), P = 0·035). The difference was more marked in the limb salvage group, even at 12 months (relative risk 1·73 (95 per cent c.i. 1·22–2·47); P = 0·006).

LMWH is superior to aspirin and Persantin in maintaining graft patency. The beneficial effect of a 3-month course of LMWH appears to continue to enhance selective graft patency for at least 1 year after surgery.

Evaluation of the effects of single-dose prostaglandin E_1 on fibrinolytic activity during major surgery

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The incidence of venous thromboembolism may be influenced by a period of reduced fibrinolytic activity following major surgery. Prostaglandin E_1 (PGE_1) has been shown to enhance fibrinolysis by inhibiting the release of plasminogen activator inhibitor (PAI-1) and promoting the release of endogenous tissue plasminogen activator (tPA).

A group of 30 patients undergoing routine total knee replacement received PGE_1 as an intravenous (i.v.) infusion ($4\,\mathrm{ng\,kg^{-1}\,min^{-1}}$) during surgery (20 cases), or subcutaneously $0{\cdot}05\,\mathrm{\mu g\,kg^{-1}}$ 2 h before surgery (five cases); five patients acted as a control group. All patients were given routine heparin thromboprophylaxis in addition. Fibrinolytic parameters were measured before, during and immediately after surgery and on days 1 and 5 thereafter. PAI-1 was significantly suppressed immediately after operation ($P < 0{\cdot}05$) in both treatment groups and tPA activity enhanced by i.v. therapy (P = 0·0065) after surgery. There were no changes in global coagulation times in either group. No serious adverse events were noted.

In conclusion, i.v. PGE_1 may be a useful adjunct in preventing fibrinolytic shutdown after major surgery, and warrants further investigation.

Sleeve arteriovenous fistula for haemodialysis as the fistula of choice

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The technique of creating an arteriovenous fistula for haemodialysis using end-to-end 'sleeve' anastomosis is presented. In all, 108 fistulas were made in this way, patients were followed for 5 years and the results analysed by life-tables. The 'sleeve' fistulas were compared with 72 fistulas made by Linton's method.

There were no early failures (within the first 24 h) in the sleeve group, and late results were good. Using Doppler ultrasonography (Bruel and Kjaer 3535), the flow of blood through the fistula was estimated and simultaneous visualization of the arteriovenous anastomosis was performed. Sleeve fistulas are considered to be the fistula of choice because of the ease of creation, and good early and late results.

Saphenous vein or polytetrafluoroethylene graft for access in haemodialysis

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Some 20–30 per cent of patients on regular haemodialysis need secondary procedures for the maintenance of vascular access. A consensus about which graft material should be used for such access is absent.

In a prospective study, therefore, the primary and secondary patency rates and complications (infection, puncture bleeding and development of aneurysms and venous hypertension) of 23 saphenous vein and 40 polytetrafluoroethylene (PTFE) prostheses (31 reinforced; nine stretch GORE-TEX) implanted as loop arteriovenous fistulas in the forearms of 48 patients in the period 1990–1992 were investigated. All patients had preoperative duplex screening of the arm vessels.

Four grafts (three PTFE, one vein) occluded before dialysis started (primary failure). There were nine early postoperative (<30 days) complications with PTFE prostheses, compared with two involving vein grafts ($P<0{\cdot}05$). In four patients of the vein group complications occurred at the donor site. During the follow-up period (mean 9 months), 26 surgical interventions were necessary in 16 PTFE prostheses because of complications compared with 14 revisions in nine vein grafts. Some 43 per cent of the vein grafts remained without any complication *versus* 35 per cent of PTFE grafts. The cumulative secondary patency rates for the vein and PTFE grafts at 0·5, 1, 2 and 3 years were 68 *versus* 70 per cent, 68 *versus* 64 per cent, 59 *versus* 57 per cent and 47 *versus* 57 per cent. The primary patency rates, including primary failure in the analysis, were better for the vein grafts than for the PTFE fistulas (62 *versus* 31 per cent after 1 year).

In view of the equal secondary patency rates for vein and PTFE grafts and the problems inherent in vein harvesting against a higher occlusion tendency of PTFE prostheses, no clear preference for vein or PTFE loop fistulas in dialysis access surgery is justified.

Transcutaneous oximetry, laser Doppler fluxmetry and capillary microscopy: reproducibility in patients with advanced atherosclerotic disease of the lower extremity

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Non-invasive methods of studying the microcirculation have been advocated in patients with advanced peripheral vascular disease to assess skin viability. A prerequisite for such tests is reproducibility of results within an individual patient and between patients. This study was performed to evaluate the reproducibility of three methods: transcutaneous oxygen tension (*P*tco$_2$) measurement, diode laser Doppler fluxmetry (dLDF) and capillary microscopy (CM).

Repeated measurements were performed in 20 patients with rest pain or severe disabling intermittent claudication (ankle:brachial pressure index $<0{\cdot}5$). *P*tco$_2$ was measured on the dorsum of the foot, and measured under baseline conditions, during 4 min of oxygen inhalation and after 3 min of tourniquet occlusion. dLDF was performed on the palmar skin of the hallux, at rest and after 3 min of occlusion. CM was performed at the nailfold of the hallux: capillary density, morphological changes of the capillaries and perfusion with fluorescein were studied.

The *P*tco$_2$ results after oxygen inhalation were reproducible and allowed for differentiation in the severity of disease. Resting *P*tco$_2$ seemed less valuable. Some dLDF results are highly reproducible, but only resting flux and the flux increase rate after tourniquet occlusion discriminated between the severity of skin ischaemia in both diabetics and non-diabetics. CM was very reliable as performed by one observer. Capillary morphology score allowed for severity grading, whereas capillary density seemed to be influenced by the presence or absence of diabetes. Only those tests with adequate reproducibility and discriminatory ability should be used to evaluate surgical procedures or to determine amputation levels.

Stapler technique for establishment of arteriovenous fistula

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Arteriovenous forearm fistulas (AVFs) for maintaining chronic blood dialysis are usually made by a suture technique. In the authors' clinic this procedure takes about 15–20 min. In a comparative study in 92 patients the routine suture technique was used in 44 procedures and a stapler in 104 for creation of AVF.

The tiny stapler devices with vacuum fixation of the vessels are now produced in the Ukraine. The usual time for fistula creation was <2 min.

While the patency rate was 100 per cent in the stapled group, thromboses did occur in the hand-sutured group, the difference being statistically significant ($P<0{\cdot}05$). The stapler technique can also be used for internal mammary artery coronary bypasses. The use of staplers could be worthwhile in many microvascular procedures where it is more rapid than hand-sewn anastomotic techniques.

Peripheral venous disorders in vascular symptom-free patients with Behçet's disease

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The aim of this study was to investigate venous system involvement in patients with Behçet's disease who were free of vascular symptoms. Two groups of patients were assessed with non-invasive venous techniques. Assessment consisted of venous Doppler and photoplethysmographic (PPG) venous reflux examination of veins of the lower extremities. The first group included 34 patients with Behçet's disease who were free of vascular symptoms and the control group consisted of 26 healthy individuals. Doppler ultrasonography was used to determine venous obstruction and insufficiency. After pneumatic calf compression, the venous return time of the blood content of the leg skin to the baseline level was defined as the prebaseline time (PBT) by PPG. Patients with PBT under 20 s was considered as having venous insufficiency. Venous insufficiency was detected in 22 of 68 legs in the Behçet's group and in seven of the 52 legs in the control group using Doppler ($P<0{\cdot}01$). Twenty of the Behçet's disease group and six of the controls had a PBT lower than 20 s ($P<0{\cdot}01$). PBT in the Behçet's disease and the control groups for the right leg was 23·6 *versus* 30·6 s ($P<0{\cdot}03$) and 27·7 *versus* 30·6 s for the left leg, respectively (*P* not significant). Deep vein thrombosis was detected in three patients with Behçet's disease, whereas none of the controls was shown by Doppler to have disease (*P* not significant).

We conclude that vascular symptom-free patients with Behçet's disease have a higher incidence of silent venous disorders than the healthy population.

Non-invasive peripheral arterial system assessment of vascular symptom-free Behçet's disease

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The aim of the present study was to determine the incidence of peripheral arterial disorders in vascular symptom-free Behçet's disease. Two groups of patients were studied. The first group consisted of 29 patients with the condition and the second group of 26 healthy individuals as a control group. Both groups underwent non-invasive peripheral arterial examinations consisting of Doppler, segmental pressure measurements and the determination of ankle brachial pressure index (ABPI) and femorobrachial pressure index (FBPI). The ABPI for the dorsalis pedis artery was $<1{\cdot}00$ in 26 legs of Behçet's group compared with nine legs in the control group ($P<0{\cdot}01$). The ABPI for the posterior tibial artery was $<1{\cdot}00$ in 12 legs in Behçet's group and in none of the controls ($P<0{\cdot}01$). The FBPI was significantly higher in the control group compared with the Behçet's disease group (1·32 *versus* 1·23 for the right leg, $P<0{\cdot}05$, 1·30 *versus* 1·22 for the left leg, $P<0{\cdot}03$).

It is concluded that the vascular symptom-free Behçet's disease has a significant incidence of arterial involvement. This patient group might benefit from screening on a routine basis.

Long-term results of the treatment of postphlebitic syndrome with the Felder operation

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The postphlebitic syndrome is an important social problem, because of the frequency of the disease and difficulties of treatment Some 3 per cent of the Polish population suffer from this disease Many operative methods are used in the treatment of grade I postphlebitic syndrome In the authors' opinion the most useful procedure is the Linton operation with Felder modification. From 1983 to 1991, 93 patients with postphlebitic syndrome were operated on In three cases both limbs were treated In each case a Linton operation with Felder modification was performed. The patients' ages ranged from 28 to 77 (mean 47) years Duration of the disease was from 1 to 33 years. Ulcerations were present in 63 cases before operation The complications in the perioperative period were: deep vein thrombosis, two patients, marginal necrosis of the skin, five, wound infection, 11. Recurrent ulceration, smaller and less trouble, was observed in ten cases. In patients with recurrent ulceration descending venography was performed. In five patients incompetent valves were present in the deep venous trunk. Four of this group underwent transplantation of a segment of brachial vein with sufficient valves, in the other transposition of a vein trunk was done. It is necessary to consider coexisting insufficiency of valves in the iliac and femoral trunk when the Felder operation is unsuccessful.

Strategy for arteriovenous fistulas as vascular access in haemodialysis

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Diligent use of the patient's own blood vessels and a clear distal-to-proximal strategy in establishing arteriovenous (AV) fistulas are key points in vascular access surgery for haemodialysis The snuff-box fistula should be the access of first choice, followed by the Brescia–Cimino fistula Proximal upper-extremity fistulas (brachiocephalic or brachiobasilic) should be established only if these peripheral fistulas fail Graft fistulas should be reserved for patients in whom all autologous veins have been used.

The authors' experience pertains to 487 AV fistulas performed over a period of 17 years. In all, 86·7 per cent of patients referred for primary vascular access surgery were suitable for the creation of a peripheral direct AV fistula. After one or several additional fistulas in cases where the primary access failed, 73·6 per cent of all unselected patients are still on maintenance haemodialysis with one of these peripheral AV fistulas

	No.	Patency rate (%)		
		1 year	2 years	3 years
Peripheral fistula				
Snuff-box	216	74	67	64
Brescia–Cimino	148	65	61	60
Upper-extremity fistula				
Brachiobasilic	55	78	74	
Brachiocephalic	25	70	60	
Interposition graft	43	74	57	

These results seem to support this step-by-step strategy Use of the native vessels progressing from the snuff-box fistula to use of the upper-extremity veins should be preferred to implantation of interposition grafts.

Heterogeneous growth responses of human vascular smooth muscle: an insight into restenosis

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Variation between individuals modelled in vascular smooth muscle cell (VSMC) hyperplasia *in vitro* may provide insights into the reasons why some, but not all, patients develop restenosis. In response to a standard 15 per cent fetal calf serum-stimulated 14-day cell growth assay, a 42 per cent coefficient of variation in growth rates is noted between different human VSMC lines from patients with restenosis and controls (n = 120) However, there was no correlation between increased growth rate and restenosis Heterogeneity is also prominent in the response of VSMC lines to growth inhibition

Inhibitor	No.	Median (range) inhibition	Coefficient of variation
Heparin (100 μg ml^{-1})	47	14·9 (0–90)	22·3
Fenofibrate (100 μM)	18	53·0 (30–68)	4·5
Amlodipine (10 μM)	16	29·0 (21–40)	5·2

Values are percentages

Cell lines varied most in response to heparin, cell lines from patients with restenosis were relatively resistant to heparin inhibition (median 8 per cent (95 per cent confidence interval 2–25 per cent)) in comparison to patients undergoing primary bypass (median 22 per cent (95 per cent confidence interval 15–44 per cent); P < 0·001, Mann–Whitney U test).

Heterogeneity in growth response of human VSMC to inhibitors *in vitro* may reflect the variable propensities to restenosis observed in patients *in vivo*, and may account for variable responses to agents in clinical trials aimed at preventing restenosis

Protection against no reflow after ischaemia

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The aim of this study was to demonstrate no reflow in skeletal muscle and to assess the benefit of allopurinol and manganese superoxide dismutase (MNSOD) The cremaster of 40 Sprague–Dawley rats was isolated the right was used for experimental manipulation and the left as a control The rats were separated into five groups: group 1 were subjected to 5 h ischaemia, group 2 had 5 h ischaemia and then 90 min reperfusion, groups 3–5 had 5 h ischaemia followed by 90 min reperfusion, but group 3 had 0·9 per cent saline, group 4 had allopurinol and group 5 had MNSOD after the period of ischaemia but before reperfusion. Responses to electrical field stimulation and postischaemic fluorescein dye perfusion were used to assess muscle injury in the treatment and control groups. Isometric tension in equivalent muscle strips was measured in an organ bath system The contractile force developed, expressed as a percentage of control, is shown

	Group 1	Group 2	Group 3	Group 4	Group 5
Potassium chloride	72(13)	31(13)*	28(9)	74(10)†	72(12)†
Twitch	57(13)	15(8)*	15(5)	48(15)†	56(9)†
Tetanus	68(15)	23(7)*	23(7)	55(17)	66(10)†

Values are mean(s.e.m.). *P < 0·05 *versus* group 1, †P < 0·05 *versus* group 2 (Mann–Whitney U test)

This study demonstrates that 5 h ischaemia produces a 50 per cent reduction in skeletal muscle function and further deterioration occurs (85 per cent functional loss) after 90 min reperfusion However, treatment with MNSOD before restoration of flow protects function and circulation Allopurinol shows a similar but lesser effect.

Preventing reperfusion injury in skeletal muscle

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The aim of this study was to reduce skeletal muscle reperfusion injury using tumour necrosis factor alpha (TNF-α), D-factor and manganese superoxide dismutase (MNSOD). The protective effects of each agent were compared by measuring muscle function and blood vessel diameter (*in vivo* videomicroscopy) in treatment and control groups.

The right cremaster muscle was isolated in 40 Sprague–Dawley rats and ischaemia induced for 5 h; this was followed by 90 min reperfusion. Arteriolar diameters were measured before and during ischaemia and reperfusion.

Isometric tension in response to electrical field stimulation and potassium chloride was measured in an organ bath

	Saline	MNSOD before	MNSOD after	TNF-α	D-factor
Tetanus	23(7)	102(18)*	66(10)*	35(10)	28(19)
Twitch	15(5)	102(24)*	56(9)*	34(11)	15(7)
Potassium chloride	32(8)	120(22)*	72(12)	38(15)	21(11)

Values are mean(s e m.) maximal tension of right cremaster as a percentage of the control (left cremaster) $*P < 0\ 05$ *versus* saline group (Mann–Whitney *U* test)

In conclusion, MNSOD confers significant protection from reperfusion injury on skeletal muscle, particularly if given before the ischaemic insult, but TNF-α and D-factor do not have such an effect in this model

Surgical treatment of the post-thrombotic syndrome: improvement of the Linton operation by use of piracetam

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In 1938, Linton proposed a technique for the treatment of patients affected by the post-thrombotic syndrome (PTS). However, more than 50 per cent of the patients developed some degree of postoperative cutaneous complications skin necrosis or epidermolysis A total of 176 Linton operations were performed at this centre during the past 8 years. The first group (1) of 60 Linton procedures was performed without protection from a low molecular weight heparin (LMWH). Of these patients 17 (28 per cent) developed cutaneous complications and one had a pulmonary embolism. A LMWH was then used systematically in a second series of patients (group 2) There was an increase in cutaneous complications, 31 of these 70 patients (44 per cent) developed skin necrosis (group 2 *versus* 1· $\chi^2 = 3{\cdot}53$, $P < 0\ 07$) However, 58 per cent of a subgroup of 40 patients with venous ulcerations had postoperative skin necrosis ($\chi^2 = 4{\cdot}24$, $P < 0\ 04$) Finally, a combination of piracetam and LMWH was used in group 3 of 46 patients undergoing Linton operations Four (9 per cent) had postoperative skin necrosis (group 3 *versus* 2. $\chi^2 = 16\ 69$, $P < 0\ 0001$) Piracetam decreased the incidence of skin necrosis 6 7 times in the absence of venous ulceration ($\chi^2 = 5{\cdot}12$, $P < 0\ 03$) and 4·1 times in the presence of ulceration ($\chi^2 = 10\ 51$, $P < 0\ 002$). It is suggested that a standardized Linton operation is a satisfactory surgical treatment of PTS. Venous ulcerations heal quickly The high cutaneous complication rate reported in the literature can be reduced by using a combination of piracetam and LMWH

Negative angiography in subarachnoid haemorrhage

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Between 10 and 20 per cent of patients with a proven subarachnoid haemorrhage (SAH) will have a normal cerebral angiogram. The prognosis is believed to be good. Given the risks of rebleeding from an undetected aneurysm, it is important to ensure that the arteriogram is truly negative before assigning a patient to this group The aim of this study was to review experience with repeat arteriography over a 2-year period

All patients with proven SAH had their case notes and radiological investigations reviewed between 1 January 1990 and 1 April 1992. SAHs secondary to a brain tumour, trauma or primary intracerebral bleed were excluded. Patients with an initial negative or equivocal angiogram were classified according to the original report and the repeat angiograms then reviewed without knowledge of the original report.

There were 216 proven SAH cases of which 172 (79 6 per cent) had an aneurysm identified, while 44 (20·3 per cent) cases were either normal or equivocal for the presence of an aneurysm Thirty of these patients underwent repeat arteriography and an aneurysm was demonstrated in ten. Three of these were from the initial entirely normal group

In conclusion, repeat arteriography is recommended in proven SAH even when the initial study is normal.

Central venous miniport implanted with a new surgical technique on the distal upper arm

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A new miniport system was used for central venous access in a prospective study including 61 patients Fifteen patients had the port positioned on their forearm and 22 on the chest wall The remaining 24 patients had miniports implanted by a new technique on the distal upper arm. The basal or brachial veins were dissected and the catheter implanted under local anaesthetic Using a new electromagnetic catheter tracking system, the catheter tip was positioned in the superior vena cava. When compared with radiographic detection the system predicted the position of the catheter tip accurately in 22 patients and changed surgical procedure by predicting incorrectly in two patients The miniports were used for chemotherapy and supportive treatment, including parenteral nutrition and transfusion Complications were observed in seven of the 15 patients with a proximal forearm port and four of the 22 patients with the chest wall port No complications were observed in patients who had implantation of the port into the distal upper arm.

As a result of this prospective study, implantation of miniports was carried out in the distal upper arm in 82 patients With a mean expected system function of 152 (range 35–485) days the complication rate was 4 per cent (two infections, one paravasation, and one incurable pain). As a consequence only three miniports had to be removed

Intravenous digital subtraction angiography *versus* computed tomography in assessment of abdominal aortic aneurysm

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The aim of this study was to compare the accuracy of intravenous digital subtraction angiography (DSA) and computed tomography (CT) in the preoperative assessment of abdominal aortic aneurysm (AAA)

Patients who had undergone elective AAA repair within the past 3 years were identified and their case notes and preoperative radiology reviewed. A total of 127 patients were identified: 103 had had preoperative DSA, 118 CT and 94 had had both Preoperative radiology reports were compared with operative findings and the sensitivity and specificity of the two investigations compared

	Renal artery involvement		Iliac artery involvement	
	DSA	CT	DSA	CT
Involvement	98 of 103 (95)	105 of 118 (89)	158 of 202 (78)	178 of 222 (80)
Sensitivity	0·60	0·83	0·75	0 56
Specificity	0·99	0·90	0 79	0·88
False positive	1 (4)	11 (52)	32 (47)	20 (40)
False negative	4 (14)	2 (2)	12 (9)	24 (14)

Values in parentheses are percentages

DSA and CT are both useful investigations in the preoperative assessment of aortic aneurysms. This study showed CT to have a higher sensitivity than DSA in the prediction of renal artery involvement This, however, was at the expense of a very high false-positive rate. DSA was far more specific than CT, though less sensitive, and missed 40 per cent of suprarenal aneurysms

Neither investigation is a good predictor of iliac involvement, both having high false-positive rates This is possibly because of underestimation of aneurysm extent by the surgeon, and the reporting of ectatic arteries as aneurysmal by the radiologist DSA gave additional information about distal occlusive disease and run-off which was not available with CT Both DSA and CT are useful investigations, but both have their limitations. Vascular surgeons should be aware of these when interpreting their results

Abdominal aortic aneurysm: 10-year population study in Glasgow

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A total of 2936 cases of aortic aneurysm admitted to Glasgow hospitals between January 1980 and December 1989 were studied. Information was obtained first from Scottish Morbidity Records 1, Scottish Hospital Inpatients Statistics, and the accuracy assessed by detailed inspection of 500 case notes evenly distributed throughout the study period. The data from 489 of these matched the Scottish Morbidity Records data which were therefore accurate in 97·8 per cent of these cases.

Of the 2936 patients, 852 (29·0 per cent) had more than one admission with the same diagnosis in the same year and of the remaining 2084, 169 (8·1 per cent) had thoracic aneurysm. After correction for these findings, the remaining 1915 patients with abdominal aortic aneurysm (AAA) were further studied Of these, 618 (32·3 per cent) were women, giving a male to female ratio of approximately 2·1, which remained constant for each year of the study The mean(s.d , s e m) age of the study population increased from 70·3(9·0, 0·74) years in 1980 to 72·3(9·2, 0·53) years in 1989. There was a significant increase in the percentage of patients over the age of 75 years (from 17·4 per cent (25 of 144) in 1980 to 28·8 per cent (86 of 299) in 1989) Some 27·1 per cent of the patients (519 of 1915) had ruptured aneurysm. Hospital mortality rate for all patients with AAA was 25·4 per cent (486 of 1915) 15·2 per cent (211 of 1389) for intact and 53·2 per cent (275 of 517) for ruptured AAA, including unoperated cases This mortality rate for patients at Glasgow Royal Infirmary, the location of the only full-time vascular unit in the city which accounted for 713 patients (37·2 per cent) of the whole study population, was lower for both ruptured and intact AAA compared with the other Glasgow hospitals The figures were 40·5 per cent (64 of 158) for ruptured and 7·9 per cent (44 of 555) for intact AAA in the Royal Infirmary compared with 58·8 per cent (211 of 359) and 19·7 per cent (166 of 843) in the other hospitals.

Allowing for improved diagnostic techniques and clinical awareness of the disease, there seems to be an increase in the incidence of AAA in Glasgow, and more women with the condition than expected The figures support the claim that vascular surgery should where possible be managed by fully trained vascular surgeons.

Vacuum compression therapy to ischaemic lower limbs

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A vacuum compression therapy device exerting alternating negative and positive pressures was used on 13 consecutive patients with chronic lower-limb ischaemia Lack of rest pain was used to assess the effects on the limb's venous blood quality and capillary flow Toe pulse oximetry and measurements of femoral venous blood gases and lactate were performed at three points. before, immediately after and 15 min after a short session of vacuum compression therapy There was evidence of initial deterioration in levels of blood gases and lactate immediately after the end of the session followed by significant improvement 15 min later

Mean(s.e.m) values before and 15 min after were compared: oxygen saturation in the toes increased from 94·3(0·52) to 97·8(0·36) per cent ($P = 0·002$); venous partial pressure of oxygen increased from 4·1(0·13) to 4·6(0·18) kPa ($P = 0·003$), venous partial pressure of carbon dioxide was hardly altered from 6·57(0·15) to 6·61(0·17) kPa ($P = 0·003$), venous hydrogen ion concentration decreased from 41·6(0·68) to 40·2(0·63) ($P = 0·003$), and venous lactate concentration decreased from 1·0(0·08) to 0·91(0·1) mmol l^{-1} ($P = 0·004$). No patient developed complications and eight experienced warmer feet for a mean(s e m) of 5·5(0·53) h following the therapy It is therefore suggested that vacuum compression therapy may improve capillary circulation of ischaemic limbs. The initial asymptomatic biochemical deterioration of the local venous blood quality may be attributed to a capillary washout phenomenon and/or a tourniquet effect of the device's rubber cuff over the patient's thigh. Further studies monitoring clinical criteria may be essential to establish the objective benefits of vacuum compression therapy in peripheral vascular disease.

Efficacy of rifampicin-impregnated graft in reducing methicillin-resistant *Staphylococcus aureus* vascular graft infection in a sheep model

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Methicillin-resistant *Staphylococcus aureus* (MRSA) is the most common infecting organism in the authors' experience of vascular graft infection The aim was to study the efficacy of rifampicin-impregnated Dacron in preventing vascular graft infection after a topical inoculum of MRSA. A left carotid artery interposition graft (length 2 cm and diameter 5 mm) was placed in 20 Merino sheep under general anaesthesia. Either a standard gelatin-sealed Dacron graft (control group, $n = 10$) or a rifampicin-soaked gelatin-sealed Dacron graft (treatment group, $n = 10$) was used At the completion of operation a topical inoculum of 108 colony-forming units of MRSA was applied After 3 weeks the sheep were reanaesthetized and the grafts were harvested in a sterile fashion. Cultures were taken of the perigraft tissues, external surface and internal washings of the graft and of a graft segment In the control group 38 of 40 cultures were positive, while only 19 of 32 cultures were positive in the treatment group ($P < 0·001$) All grafts were infected on at least one culture There was a significant decrease in abscess formation in the treatment group ($P < 0·003$) There was no difference in patency rates or anastomotic disruption. None of the MRSA retrieved from the grafts had developed resistance to rifampicin

Long-term outcome of critical limb ischaemia

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Factors affecting the outcome of critical leg ischaemia need to be defined to formulate appropriate treatment options. During a 42-month period 232 critically ischaemic limbs were treated in 209 patients (median age 71 (range 42–92) years), of whom 76 (36 per cent) had diabetes mellitus Tissue necrosis was the presenting feature in 123 limbs (53 per cent) and rest pain alone in 109 (47 per cent) Overall, although the cumulative 2-year limb salvage rate was 71 per cent with a corresponding mortality rate of 27 per cent, only 36 per cent of patients remained symptom-free after 12-month follow-up Univariate analysis of pretreatment risk factors showed that advanced age, sex, diabetes mellitus, tissue necrosis or the preoperative ankle pressure did not affect limb salvage, mortality, or symptom recurrence rates Although it is possible to achieve high limb salvage rates by pursuing an aggressive approach to revascularization in critical limb ischaemia, recurrence of symptoms is common The outcome of treatment, however, is not influenced by preoperative risk factors and these should not be considered to be contraindications to revascularization.

Analysis of critical risk factors for elective aortic replacement for abdominal aortic aneurysm

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Complications and causes of mortality in 768 consecutive patients who underwent elective aortic replacement (EAR) for abdominal aortic aneurysm (AAA) during the past 12 years were analysed Age ranged from 37 to 92 years, and the male female ratio was 3:1. EAR was performed using either transperitoneal endoaneurysmorrhaphy or a retroperitoneal approach A total of 20 patients had severe chronic obstructive pulmonary disease and 1·5 per cent were on home oxygen. Some 33 per cent of patients had preoperative creatine levels above 1 3 mg dl^{-1}, 15 patients were dialysis dependent and six had had a renal transplant The perioperative mortality rate was 2·3 per cent and did not change significantly with either time or operative technique. The majority of deaths were the result of cardiac complications (56 per cent) In addition, 8 7 per cent of patients had non-fatal complications, which were equally distributed among renal, pulmonary and cardiac causes.

Cardiovascular, pulmonary and renal risk factors, complications and mortality in the last 50 consecutive patients were prospectively evaluated. Some 40 per cent had moderate to restricted pulmonary function and 50 per cent a serum creatine level greater than 1·3 mg dl^{-1} The mortality rate, causes of death and complication rate remained similar. These data show that pulmonary and renal impairment did not pose significant risks for EAR. Cardiac risk was the same, in spite of detailed cardiac evaluation by history, electrocardiogram, stress tests and selective cardiac catheterization. It is suggested, therefore that, except for significant coronary artery disease, no other risk factors should deter EAR for AAA.

Autotransfusion in aortic surgery using a new membrane cell separator

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To date, centrifugal cell separators have been used in intraoperative autotransfusion An alternative is to use filtration. The Haemocell 350 system, which employs pulsed flow and a high surface area quadruple sandwich filter, has undergone investigation.

A 0·2-μm pore size filter was studied first (n = 8). This yielded high heparin (3·2 units) levels and a low packed cell volume (PCV) (0·19, 0 16) in the reinfusate; electron micrographs revealed filter blockage. In the second phase a 0 6-μm pore size filter was used Collected blood was either washed (n = 5) or unwashed (n = 5) with saline. Filter efficiency was judged by PCV, plasma haemoglobin (Hb), D-dimer and heparin washout. Two units of collected blood were processed with each filter.

	Washed		Unwashed	
	Unit 1	Unit 2	Unit 1	Unit 2
PCV	0 20	0 13	0 25	0 22
	(0 20–0 26)	(0 12–0 17)	(0 24–0 35)	(0 15–0 23)
Hb	230	180	528	286
(mg dl^{-1})	(42–337)	(75–320)	(230–1390)	(216–841)
D-dimer	4	8	32	32
(μg ml^{-1})	(4–16)	(4–16)	(16–64)	(16–64)
Heparin	1 6	2 4	3 0	3 0
concentration (units ml^{-1})	(1 2–5 1)	(1 3–6 8)	(2 0–5 2)	(1 2–5 0)
Amount of	464	1039	462	882
heparin (units)	(342–1775)	(651–3230)	(242–775)	(458–1345)
Processed	550	580	540	545
volume (ml)	(480–570)	(470–620)	(490–654)	(480–620)
Reinfused	356	540	196	446
volume (ml)	(346–446)	(496–626)	(186–206)	(336–488)

Values are median (range)

Filtration and saline washing reduced heparin, D-dimer and haemoglobin concentrations, but increased the quantity of reinfusate and decreased its PCV In both groups a considerable amount of heparin was present in the reinfusate. Clinical application of this system should be confined to cardiovascular surgery where the effect of heparin can be reversed with protamine.

Ne–He laser radiation in treatment of crural ulcerations in patients with post-thrombotic syndrome and diabetic angiopathy

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Crural ulcerations resulting from post-thrombotic syndrome and diabetic angiopathy were treated with 0·25 per cent silver nitrate solution and moist applications of antibiotics effective against cultured microflora In addition, crural ulcerations were irradiated in randomized patients with a Ne–He laser The field of ulcerations was planimetrically measured by contact copies on sterile foil strips. Comparison of epithelialization times of ulceration enabled the determination of the effectiveness of the procedure. No patient showed arterial disorders in the lower extremities, 90 limbs were treated, including 70 with post-thrombotic syndrome and 22 with diabetic angiopathy Differences were not found between healing rates of irradiated and non-irradiated ulcerations in patients with post-thrombotic syndrome Healing time of ulcerations in diabetic patients was shorter than in those with post-thrombotic syndrome Healing time of irradiated ulcerations in the limbs of diabetic patients was statistically shorter The results obtained encourage the use of the Ne–He laser in the treatment of diabetic legs.

Lipid peroxidation in spinal cord ischaemia and reperfusion injury

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Changes in lipid peroxidation in a rabbit model of typical spinal cord injury are reported Secondary paraplegia was induced by abdominal aortic occlusion. After 40 min of occlusion, the malonyldialdehyde (MDA) level and water content in the T7–T8 and L3–L4 regions increased, while superoxide dismutase (SOD) decreased. After 30 min, and 2, 4 and 24 h of reperfusion, the MDA level and water content continued to increase ($P <$ 0·001), MDA reached a peak after 4 h of reperfusion, while SOD decreased (compared with normal control levels and those measured during the period of ischaemia, $P <$ 0·001) The changes in SOD and MDA levels in the spinal cord correlated negatively (T7–T8. $r = -0·7$, $P <$ 0 01; L3–L4, $r = -0·98$. $P <$ 0 001). The MDA levels and water content correlated with each other positively (T7–T8 r = 0 94, $P <$ 0 01; L3–L4. r = 0 76, $P <$ 0 05) It may be inferred that lipid peroxidation played an important role in the deterioration of hindlimb function and pathological changes of the cord after spinal ischaemia and reperfusion, furthermore, suppressing the production of free radicals and enhancing antioxidant activity in local tissues might be of benefit in preventing secondary injury

Accelerated peripheral thrombolysis with a pulse-spray technique

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Pulse-spray thrombolysis (PST) is a new technique of accelerated thrombolysis. This study presents experience of 23 consecutive patients, 20 with native peripheral arterial thrombosis and three with peripheral bypass graft thrombosis. The median age of the patients was 74·5 (range 35–89) years and the median duration of symptoms 6 (range 1–60) days. Severe ischaemia with sensory and motor deficit was present in 11 of 23 patients. Recombinant tissue plasminogen activator (rtPA) was used in a concentration of 0·33 mg ml^{-1} in boluses of 0·2 ml with a median total dose of 18 (range 10–35) mg. The median length of occlusion was 23 (range 4–55) cm. Complete radiological lysis was achieved in 22 of 23 cases and the median duration of lysis was 135 (range 50–1125) min which is a nine-fold reduction in the lysis time compared with results of conventional therapy with rtPA. The median ankle.brachial pressure index improved significantly (P = 0·002, Mann–Whitney U test) from a prelysis value of 0 to a value after lysis of 0 8. PST rapidly restores vascular patency and therefore may become the treatment of choice in acute limb ischaemia including those at immediate risk of irreversible ischaemic damage, which would conventionally be treated with emergency surgical reconstruction.

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